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=> s bee venom

L1 7518 BEE VENOM

=> s l1 and polypeptide

L2 502 L1 AND POLYPEPTIDE

=> s l2 and 8 Kd

L3 0 L2 AND 8 KD

=> s l2 and 8

L4 55 L2 AND 8

=> s l4 and Kd

L5 3 L4 AND KD

=> dup remove l5

PROCESSING COMPLETED FOR L5
L6 2 DUP REMOVE L5 (1 DUPLICATE REMOVED)

=> d l6 1-2 cbib abs

L6 ANSWER 1 OF 2 MEDLINE
88082757 Document Number: 88082757. PubMed ID: 2446869. Photoaffinity
labeling of the K⁺-channel-associated apamin-binding molecule in smooth
muscle, liver and heart membranes. Marqueze B; Seagar M J; Couraud F.
(Laboratoire de Biochimie, Centre National de la Recherche Scientifique
Unite Associee 1179, Marseille-France.) EUROPEAN JOURNAL OF

BIOCHEMISTRY,
(1987 Dec 1) 169 (2) 295-8. Journal code: EMZ; 0107600. ISSN: 0014-2956.
Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language:
English.

AB High-affinity binding sites for mono[125I]iodoapamin were detected in
membranes (K_d = 59 pM, B_{max} = 24 fmol/mg protein) and cultured
cells (K_d = 69 pM, B_{max} = 2.8 fmol/mg protein) from
rat heart and in membranes from guinea-pig ileum (K_d = 67 pM,
B_{max} 42 fmol/mg protein) and liver (K_d = 15 pM, B_{max} = 43
fmol/mg protein). Binding was stimulated by K⁺ ions (K_{0.5} = 0.3-0.5 mM).
Covalent labeling with arylazide [125I]iodoapamin derivatives showed that
smooth muscle, liver and heart binding molecules are associated with a
85-87-kDa **polypeptide**. A second strongly labeled 57-kDa
component was identified in liver membranes only.

L6 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
87133589 Document Number: 87133589. PubMed ID: 3028799.
Receptor-mediated

endocytosis of apamin by liver cells. Strong P N; Evans W H. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1987 Mar 2) 163 (2) 267-73. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB The binding and uptake of the **bee venom** toxin apamin, by guinea-pig and rat liver were studied. Guinea-pig liver plasma membranes contain inhibitable, high-affinity binding sites for [125I]monoiodoapamin: $K_d = 12.6 \pm 0.8$ pM (SE); $B_{max} = 4.2 \pm 0.2$ fmol/mg protein. No binding sites for [125I]monoiodoapamin on rat liver plasma membranes were detected in agreement with the absence of a physiological response to the toxin by rat hepatocytes. [125I]Monoiodoapamin, injected into the portal vein of guinea-pigs, was recovered in an undegraded form in a liver endosome fraction. The uptake of [125I]monoiodoapamin by rat livers was less than 4% of that taken up

by guinea-pig livers and there was little evidence of radiolabelled toxin appearing in isolated rat endocytic vesicles. Inhibitable, high-affinity binding sites for [125I]monoiodoapamin were also identified on isolated guinea-pig liver endosomal membranes; $K_d = 10.6 \pm 3.3$ pM; $B_{max} = 2.5 \pm 0.6$ fmol/mg protein. No inhibitable apamin binding sites were detected on rat endosomal membranes. Plasma membranes and endosomal membranes isolated from guinea-pig liver showed a similar spectrum of **polypeptides** to that previously reported for plasma membranes and endosomal membranes isolated from rat liver. The enzymatic composition of guinea-pig endosomes was also similar to that previously reported for rat endosomes. The results indicate that apamin was internalised by receptor-mediated endocytosis by guinea-pig liver cells in an analogous manner to that already shown for a variety of endogenous ligands.

=> s spertini f?/au

L7 414 SPERTINI F?/AU

=> s 17 and bee venom

L8 45 L7 AND BEE VENOM

=> dup remove 18

PROCESSING COMPLETED FOR L8

L9 19 DUP REMOVE L8 (26 DUPLICATES REMOVED)

=> d 19 1-19 cbib abs

L9 ANSWER 1 OF 19 MEDLINE DUPLICATE 1
2001226583 Document Number: 21142832. PubMed ID: 11207323.

Antigen-independent suppression of the allergic immune response to **bee venom** phospholipase A(2) by DNA vaccination in CBA/J mice. Jilek S; Barbey C; **Spertini F**; Corthesy B. (Division of Immunology and Allergy, R & D Laboratory, Centre Hospitalier

Universitaire

Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2001 Mar 1) 166

(5) 3612-21. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Phospholipase A(2) (PLA(2)) is one of the major honey **bee venom** allergens for humans. To assess the long-term prevention of allergic reactions by DNA vaccination, a PLA(2)-CBA/J mouse model was employed using empty or PLA(2) sequence-carrying DNA plasmids. Early skin application of either DNA construct before (prophylactic approach) or after (therapeutic approach) sensitization with PLA(2)/alum led to reduced

PLA(2)-specific IgE and IgG1 titers at 7 mo, with concomitant rise in IgG2a and IgG3. Splenocytes recovered at 5-6 mo after the last DNA administration exhibited a sustained IFN-gamma and IL-10 secretion and reduced IL-4 production. Recall challenge with PLA(2) boosted IFN-gamma and IL-10 secretion, suggesting the reactivation of quiescent memory Th1 lymphocytes. Mice from the prophylactic groups were fully protected against anaphylaxis, whereas 65% of the animals recovered in the therapeutic groups. Th1-polarized immune responses were also active in mice vaccinated with an empty plasmid 32 wk before sensitization with another Ag (OVA). This is the first demonstration that the Ag-coding sequence in DNA vaccine is not necessary to promote immune modulation in naive and sensitized animals for a prolonged period, and has relevance

for the understanding of the innate and induced mechanisms underlying gene immunotherapy in long-term treatment of allergy.

L9 ANSWER 2 OF 19 MEDLINE DUPLICATE 2
2001242064 Document Number: 21242713. PubMed ID: 11344362. Api m 6: a new

bee venom allergen. Kettner A; Hughes G J; Frutiger S; Astori M; Roggero M; **Spertini F**; Corradin G. (Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (2001 May) 107 (5) 914-20. Journal

code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Characterization of the primary structure of allergens is a prerequisite for the design of new diagnostic and therapeutic tools for allergic diseases. OBJECTIVE: The purpose of this study was the identification and characterization of a low-molecular-weight, IgE-binding, **bee venom** (BV) allergen. METHODS: BV proteins were separated by using size exclusion chromatography and HPLC. IgE antibody binding to purified proteins was analyzed by means of immunoblotting, and T-cell response was analyzed by means of

proliferation assay. Amino acid sequence was determined with 2 approaches, namely Edman degradation and carboxy terminal analysis with mass spectrometry.

RESULTS:

Api m 6, which migrated as an 8-kd band in SDS-PAGE, was frequently (42%) recognized by IgE from BV-hypersensitive patients. In addition, PBMCs

from BV-hypersensitive patients, as well as from a normal control subject, proliferated in response to this allergen. Api m 6 exists as 4 isoforms

of 7190, 7400, 7598, and 7808 d, respectively. Amino acid sequences obtained from HPLC-purified preparations revealed that the isoforms were constituted of a common central core of 67 residues, only differing in

the amino- and carboxy-terminal ends. Api m 6 showed no significant sequence

homology with known proteins. CONCLUSIONS: We have identified and sequenced a new BV allergen that elicits a strong IgE and T-cell response in a large number of BV-hypersensitive patients. Api m 6 should be considered in the diagnostic and therapeutic approach of BV immunotherapy on the basis of peptides or recombinant proteins.

L9 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
2001:199768 Document No.: PREV200100199768. Antigen-independent suppression of

the allergic immune response to **bee venom** phospholipase A2 by DNA vaccination in CBA/J mice. Cortesey, Blaise (1); Jilek, Samantha (1); Barbey, Catherine (1); **Spertini, Francois (1)** . (1) Hopital Orthopedique, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (February, 2001) Vol. 107, No. 2, pp. S325. print. Meeting Info.: 57th Annual Meeting of the American Academy of Allergy, Asthma and Immunology New Orleans, Louisiana, USA March 16-21, 2001 ISSN: 0091-6749. Language: English. Summary Language: English.

L9 ANSWER 4 OF 19 MEDLINE DUPLICATE 4
2000483268 Document Number: 20432339. PubMed ID: 10975871. Inducing tolerance by intranasal administration of long peptides in naive and primed CBA/J mice. Astori M; von Garnier C; Kettner A; Dufour N; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2000 Sep 15) 165 (6) 3497-505. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To assess the capacity of a peptide-based immunotherapy to induce systemic tolerance via the nasal route, we designed three long overlapping peptides of 44-60 aa covering the entire sequence of phospholipase A2 (PLA2), a major **bee venom** allergen. Both prophylactic and therapeutic intranasal administrations of long peptides to PLA2-hypersensitive CBA/J mice induced specific T cell tolerance to the native allergen. In prophylactic conditions, this tolerance was marked by a suppression of subsequent specific IgE response, whereas the therapeutic approach in presensitized mice induced a more than 60% decrease in PLA2-specific IgE. This decline was associated with a shift in the cytokine response toward a Th1 profile, as demonstrated by decreased PLA2-specific IgG1 and enhanced IgG2a levels, and by a decline in the specific IL-4/IFN-gamma ratios. T cell transfer from long peptide-tolerized mice to naive animals abrogated the expected anti-PLA2 IgE and IgG1 Ab response, as well as specific T cell proliferation, but enhanced specific IgG2a response upon sensitization with PLA2. These events were strongly suggestive of a clonal anergy affecting more profoundly Th2 than the Th1 subsets. In conclusion, these results demonstrate that allergen-derived long peptides delivered via the nasal mucosa may offer an alternative to immunotherapy with native allergens without the inherent risk of systemic anaphylactic reactions. Moreover, long peptides, in contrast to immunotherapy strategies based on short peptides, have the advantage of covering all potential T cell epitopes, and may represent novel and safe tools for the therapy of allergic diseases.

L9 ANSWER 5 OF 19 MEDLINE DUPLICATE 5
2000386468 Document Number: 20354865. PubMed ID: 10898500.
Allergen-derived long peptide immunotherapy down-regulates specific IgE

response and protects from anaphylaxis. von Garnier C; Astori M; Kettner A; Dufour N; Heusser C; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jun) 30

(6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country:

GERMANY: Germany, Federal Republic of. Language: English.

AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J mice were sensitized with low dose alum-adsorbed phospholipase A2 (PLA2), a major **bee venom** allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides (44- to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long peptide mixture were fully protected from anaphylaxis. This indicated

that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L9 ANSWER 6 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:192482 The Genuine Article (R) Number: 287WR. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2 derived long peptides in **bee venom** hypersensitive patients. **Spertini F (Reprint)**; Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin

G. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS,

MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2-derived

long peptides in **bee venom** hypersensitive patients.

Spertini, Francois (1); Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1)

Division

of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy and Clinical

Immunology.,

(Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary

Language: English.

L9 ANSWER 8 OF 19 MEDLINE DUPLICATE 6
1999221995 Document Number: 99221995. PubMed ID: 10202349. IgE and
T-cell

responses to high-molecular weight allergens from **bee venom**. Kettner A; Henry H; Hughes G J; Corradin G; Spertini F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1999 Mar) 29 (3) 394-401. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: **Bee venom** contains multiple allergens with a wide distribution of molecular weight. In contrast with conventional **bee venom** desensitization, peptide or recombinant allergen immunotherapy may have to take into account patients' individual patterns of humoral or cellular response. OBJECTIVE: To study immunoglobulin (Ig)E and T-cell responses to high-molecular weight **bee venom** allergens ≥ 50 kDa. METHODS: **Bee venom** proteins were separated by size exclusion chromatography and fractions were characterized by one and two-dimensional gel electrophoresis. IgE antibody binding to **bee venom** fractions was analysed by immunoblotting and T-cell responses by proliferation assay. RESULTS: Among 38 **bee venom** -hypersensitive patients, IgE recognition pattern of **bee venom** allergens varied greatly. IgE bound mainly to phospholipase A2 and furthermore to several proteins ≥ 50 kDa (50, 54, 69, 84 and 94 kDa). N-terminal sequences of these proteins showed no homology with known proteins. In addition, peripheral mononuclear cells from patients as well as from nonatopic donors strongly proliferated in response to those proteins. CONCLUSIONS: Although present in low amounts, high-molecular weight allergens from **bee venom** elicit strong IgE and T-cell responses, and may need to be considered as clinically relevant. Therefore, the development of peptide or recombinant protein-based immunotherapy for **bee venom** allergy may require careful characterization of such allergens.

L9 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:142906 The Genuine Article (R) Number: 165FC. Intranasal administration of long overlapping peptides from **bee venom** phospholipase A2 induces tolerance in hypersensitive CBA/J. Astori M (Reprint); vonGarnier C; Corradin G P; Spertini F. CHU VAUDOIS, DEPT IMMUNOL & ALLERGY, LAUSANNE, SWITZERLAND; UNIV LAUSANNE, INST BIOCHEM, CH-1015 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1999) Vol. 103, No. 1, Part 2, Supp. [S], pp. 192-192. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1999:136272 Document No.: PREV199900136272. Intranasal administration of long overlapping peptides from **bee venom** phospholipase A2 induces tolerance in hypersensitive CBA/J mice. Astori, M. (1); Von Garnier, C. (1); Corradin, G. P.; Spertini, F. (1). (1) Dep. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1999) Vol. 103, No. 1 PART 2, pp. S51.

Meeting

Info.: 55th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3, 1999 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language: English.

L9 ANSWER 11 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1998:176527 The Genuine Article (R) Number: YW339. Isolation and characterization of a novel 7.6 Kd allergen from **bee venom**. Astori M (Reprint); Kettner A; Frutiger S; Hughes G J; Corradin G; **Spertini F**. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1998) Vol. 101, No. 1, Part 2, pp. 697-697. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 12 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1998:154406 Document No.: PREV199800154406. Isolation and characterization of a novel 7.6 Kd allergen from **bee venom**. Astori, M.; Kettner, A.; Frutiger, S.; Hughes, G. J.; Corradin, G.; **Spertini, F.** Div. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1998) Vol. 101, No. 1 PART 2, pp. S169. Meeting Info.: 54th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Washington, DC, USA March 13-18, 1998 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language: English.

L9 ANSWER 13 OF 19 MEDLINE DUPLICATE 7
1998341973 Document Number: 98341973. PubMed ID: 9678833. Delineation of PLA2 epitopes using short or long overlapping synthetic peptides: interest for specific immunotherapy. Kammerer R; Kettner A; Chvatchko Y; Dufour N; Tiercy J M; Corradin G; **Spertini F**. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1997 Sep) 27 (9) 1016-26. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Venom immunotherapy is definitely indicated in severe systemic anaphylactic reactions to bee stings, but is not devoided of risks of anaphylaxis. Safer methods of immunotherapy need to be developed. OBJECTIVE: To delineate phospholipase A2 T-cell epitopes using short 15mer vs long 40-60mer overlapping peptides, and to approach the potential interest of a venom immunotherapy based on the use of long peptides (1-60, 51-99, 90-134) mapping the whole phospholipase A2 molecule vs a restricted number of immunodominant epitopes. METHODS: Proliferation of a CD8+ T cell depleted peripheral blood mononuclear cell fraction and short-term T-cell lines from unselected **bee venom** hypersensitive patients in response to phospholipase A2 synthetic peptides. RESULTS: Whereas T-cell proliferation to 15mer overlapping peptides was weak, T-cell response to long overlapping peptides was in contrast vigorous in all patients, mostly directed to C-terminal peptide 90-134. Our results did not support the concept of rare dominant T-cell epitopes, and disclosed T-cell responses to multiple epitopes in several patients. No

significant IgE-binding to long overlapping peptides was detected except in one patient against peptide 90-134. CONCLUSION: 15mer peptides might not be sensitive enough to fully delineate all potential T-cell epitopes scattered along the allergen. Since they do not bind IgE in vitro or only weakly, and taking into account a T-cell response frequently directed to multiple epitopes, long overlapping peptides may represent ideal tools for immunotherapy.

L9 ANSWER 14 OF 19 MEDLINE DUPLICATE 8
97400299 Document Number: 97400299. PubMed ID: 9257793. Modulation of T-cell response to phospholipase A2 and phospholipase A2-derived peptides by conventional **bee venom** immunotherapy. Kammerer R; Chvatchko Y; Kettner A; Dufour N; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1997 Jul) 100 (1) 96-103. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Immunologic mechanisms of desensitization are still incompletely understood. Safer methods of immunotherapy with reduced risks of anaphylaxis need to be developed. OBJECTIVE: To study the effects of conventional venom immunotherapy (VIT) on phospholipase A2 (PLA2)-specific T cells and on T-cell reactivity to short and long synthetic peptides that map the PLA2 molecule. METHOD: Proliferation of a CD4+ cell-enriched peripheral blood mononuclear cell fraction and cytokine secretion by T cell lines from patients hypersensitive to **bee venom** and undergoing VIT in response to PLA2 and PLA2 synthetic peptides were measured. RESULTS: T-cell proliferation in response to three synthetic peptides, 40 to 60 amino acids long and mapping the entire PLA2 molecule with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to 134) steadily increased during the first 14 weeks of VIT corresponding to the treatment period with incremental doses of antigen. These results are in contrast to the low proliferation indices obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the molecule with short peptides. At the end of VIT (after 3 to 5 years), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by a shift in the pattern of cytokine secretion by T cell lines from a T(H0)-type to a T(H1)-type pattern. CONCLUSION: After a transient increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of cytokine secretion from a T(H0)-type to a T(H1)-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 molecule appear to be efficient T cell stimulators and may represent potential candidates for peptide immunotherapy.

L9 ANSWER 15 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
96:400023 The Genuine Article (R) Number: UK861. A NOVEL 7.6 KD ALLERGEN FROM

BEE VENOM - ISOLATION AND CHARACTERIZATION. ASTORI M (Reprint); KETTNER A; FRUTIGER S; HUGHES G J; CORRADIN G; **SPERTINI F.** CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND;

INST BIOCHEM, CH-1066 EPALINGES, SWITZERLAND; CTR MED UNIV GENEVA, DEPT
MED BIOL, CH-1211 GENEVA, SWITZERLAND. FASEB JOURNAL (30 APR 1996) Vol.
10, No. 6, pp. 2764. ISSN: 0892-6638. Pub. country: SWITZERLAND.

Language:
ENGLISH.

L9 ANSWER 16 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310225 Document No.: PREV199699032581. T cell epitope mapping with short
or long synthetic peptides. Kettner, A. (1); Chvatachko, Y.; Kammerer,

R.;
Dufour, N.; Corradin, G. (1); **Spertini, F.** (1) Inst. Biochem.,
1066 Epalinges Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp.
A1479. Meeting Info.: Joint Meeting of the American Society for
Biochemistry and Molecular Biology, the American Society for

Investigative
Pathology and the American Association of Immunologists New Orleans,
Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

L9 ANSWER 17 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310226 Document No.: PREV199699032582. A novel 7.6kD allergen from
bee venom: Isolation and characterization. Astori, M.
(1); Kettner, A.; Frutiger, S.; Hughes, G. J.; Corradin, C.;
Spertini, F. (1). (1) Div. Immunol. Allergy, Cent. Hosp. Univ.
Vaudois, 1011 Lausanne Switzerland. FASEB Journal, (1996) Vol. 10, No. 6,
pp. A1479. Meeting Info.: Joint Meeting of the American Society for
Biochemistry and Molecular Biology, the American Society for

Investigative
Pathology and the American Association of Immunologists New Orleans,
Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

L9 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1995:383183 Document No.: PREV199598397483. T cell response to **bee**
venom allergens: Modulation by specific immunotherapy. Kammerer,
R. B. (1); Chvatchko, Y. (1); Kettner, A. J.; Corradin, G.; **Spertini,**
F. (1) Div. Immunol. Allergy, CHUV, Lausanne Switzerland. 9TH
INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 436. The 9th
International Congress of Immunology. Publisher: 9th International
Congress of Immunology San Francisco, California, USA. Meeting Info.:
Meeting Sponsored by the American Association of Immunologists and the
International Union of Immunological Societies San Francisco, California,
USA July 23-29, 1995 Language: English.

L9 ANSWER 19 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1995:381846 Document No.: PREV199598396146. T-cell and IgE response to
partially purified **bee venom** (BV) allergens. Kettner,
A. J. (1); Chvatchko, Y.; Kammerer, R. B.; Corradin, G.; **Spertini,**
F. (1) Inst. Biochem., Lausanne Switzerland. 9TH INTERNATIONAL
CONGRESS OF IMMUNOLOGY.. (1995) pp. 208. The 9th International Congress

of
Immunology. Publisher: 9th International Congress of Immunology San
Francisco, California, USA. Meeting Info.: Meeting Sponsored by the
American Association of Immunologists and the International Union of
Immunological Societies San Francisco, California, USA July 23-29, 1995
Language: English.

=> d his

(FILE 'HOME' ENTERED AT 14:17:20 ON 16 JUL 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 14:17:34 ON
16 JUL 2001

L1 7518 S BEE VENOM
L2 502 S L1 AND POLYPEPTIDE
L3 0 S L2 AND 8 KD
L4 55 S L2 AND 8
L5 3 S L4 AND KD
L6 2 DUP REMOVE L5 (1 DUPLICATE REMOVED)
L7 414 S SPERTINI F?/AU
L8 45 S L7 AND BEE VENOM
L9 19 DUP REMOVE L8 (26 DUPLICATES REMOVED)

=> s l4 and IgE binding

4 FILES SEARCHED...

L10 4 L4 AND IGE BINDING

=> dup remove l10

PROCESSING COMPLETED FOR L10

L11 1 DUP REMOVE L10 (3 DUPLICATES REMOVED)

=> d l11 cbib abs

L11 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
92113252 Document Number: 92113252. PubMed ID: 1730869.
Glycosylation-inhibiting factor from human T cell hybridomas constructed
from peripheral blood lymphocytes of a **bee venom**
-sensitive allergic patient. Thomas P; Gomi H; Takeuchi T; Carini C;
Tagaya Y; Ishizaka K. (La Jolla Institute for Allergy and Immunology, CA
92037.) JOURNAL OF IMMUNOLOGY, (1992 Feb 1) 148 (3) 729-37. Journal
code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States.
Language: English.

AB Human T cell hybridomas, which constitutively secrete glycosylation
inhibiting factor (GIF), were constructed from PBL of an allergic
individual who was sensitive to honey **bee venom**. PBMC
of the patient were stimulated with either denatured or cyanogen
bromide-treated **bee venom** phospholipase A2 (PLA2), and
Ag-activated cells were propagated by IL-2 in the presence of human
recombinant lipocortin I. T cells obtained in the cultures were fused

with a HAT-sensitive mutant of the human lymphoblastoid cell line CEM.
Approximately one-third of hybridoma clones constitutively secreted GIF.
The GIF-producing hybridomas were CD3+ and bore TCR-alpha beta. GIF
formed

by unstimulated hybridomas lacked affinity for **bee venom**
PLA2. Upon cross-linking of CD3, however, a majority of the GIF-producing
hybridomas formed **IgE-binding** factors and GIF, the
latter of which had affinity for **bee venom** PLA2. Both
nonspecific GIF and Ag-binding GIF from the hybridomas bound to an
immunosorbent coupled with the anti-lipomodulin mAb 141-B9. Using an
affinity-purified GIF as an immunogen, we established mouse B cell
hybridomas that secreted monoclonal anti-human GIF. In order to
characterize human nonspecific GIF, one of the GIF-producing hybridomas

was adapted to a serum-free medium, and culture supernatant was fractionated by DEAE-Sepharose column chromatography and by gel filtration. The majority of nonspecific GIF in the culture supernatant was

recovered from DEAE-Sepharose by elution of the column with 10 mM Tris-HCl

buffer, pH 8.0, containing 50 mM NaCl. Affinity-purification of GIF in the DEAE Sepharose fraction by using anti-GIF-coupled Affigel, and analysis of the purified GIF by SDS-PAGE revealed that human GIF is a single **polypeptide** chain of 14 to 15 kDa. Gel filtration of both crude and affinity-purified GIF preparations confirmed the molecular size of the cytokine.

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Executing the logoff script...

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SINCE FILE	TOTAL
ENTRY	SESSION
52.79	52.94

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TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS	4	Feb 16 TOXLINE no longer being updated
NEWS	5	Apr 23 Search Derwent WPINDEX by chemical structure
NEWS	6	Apr 23 PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS	7	May 07 DGENE Reload
NEWS	8	Jun 20 Published patent applications (A1) are now in USPATFULL
NEWS	9	JUL 13 New SDI alert frequency now available in Derwent's DWPI and DPCI

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FULL ESTIMATED COST	0.15	0.15

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=> s bee venom

2 FILES SEARCHED...
4 FILES SEARCHED...
L1 7518 BEE VENOM

=> s l1 and polypeptide

1 FILES SEARCHED...
L2 502 L1 AND POLYPEPTIDE

=> s l2 and phospholipase A2

L3 76 L2 AND PHOSPHOLIPASE A2

=> s l3 and hyaluronidase

L4 4 L3 AND HYALURONIDASE

=> dup remove l4

PROCESSING COMPLETED FOR L4
L5 2 DUP REMOVE L4 (2 DUPLICATES REMOVED)

=> d 15 1-2 cbib abs

L5 ANSWER 1 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
1998201277 EMBASE Application of free-flow electrophoresis for isolation and
purification of proteins and peptides. Loseva O.I.; Gavryushkin A.V.;
Osipov V.V.; Vanyakin E.N.. Dr. A.V. Gavryushkin, State Res. Ctr. Applied
Microbiol., Obolensk, Moscow Region 142279, Russian Federation.
Electrophoresis 19/7 (1127-1134) 1998.
Refs: 34.

ISSN: 0173-0835. CODEN: ELCTDN. Pub. Country: Germany. Language: English.
Summary Language: English.

AB Free-flow electrophoresis (FFE) has been applied to the separation and
purification of a variety of proteins and **polypeptides**:
bee venom, tumor necrosis factor, interleukin-1.beta.,
interferon-.gamma. and superoxide dismutase. FFE at constant pH and
conductivity of the carrying buffer is shown to be efficient at various
separation schemes. In some cases, the method allows us to obtain
proteins
with a purity of more than 90% at a productivity of 20-30 mg/h. An
electrophoretic apparatus with a new, multi-sectional construction of the
electrophoretic chamber and a system for cross-displacement of carrying
buffer in the chamber is described.

L5 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
94339780 EMBASE Document No.: 1994339780. Liquid chromatographic analysis
and

separation of **polypeptide** components from honey **bee**
venoms. Szokan G.; Horvath J.; Almas M.; Saftics G.; Palocz A..
Department of Organic Chemistry, Eotvos University, Eotvos, Budapest,
Hungary. Journal of Liquid Chromatography 17/16 (3333-3349) 1994.
ISSN: 0148-3919. CODEN: JLCHD8. Pub. Country: United States. Language:
English. Summary Language: English.

AB Reversed-phase HPLC on different columns with acetonitrile-water-
trifluoroacetic acid eluent system was used to characterize honey
bee venoms and to separate and determine quantitatively
its peptide components.

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(FILE 'HOME' ENTERED AT 15:52:23 ON 16 JUL 2001)

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16 JUL 2001

L1 7518 S BEE VENOM
L2 502 S L1 AND POLYPEPTIDE
L3 76 S L2 AND PHOSPHOLIPASE A2
L4 4 S L3 AND HYALURONIDASE
L5 2 DUP REMOVE L4 (2 DUPLICATES REMOVED)

=> s 12 and allergen C

L6

1 L2 AND ALLERGEN C

=> d 16 cbib abs

L6 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 2001 ISI (R)
97:726142 The Genuine Article (R) Number: XX857. Comparison of the antibody response to **bee venom** phospholipase A(2) induced by natural exposure in humans or by immunization in mice. Schneider T (Reprint); Dudler T; Annand R R; Gelb M H; King T P; Suter M. SWISS INST ALLERGY & ASTHMA RES, CH-7270 DAVOS, SWITZERLAND; UNIV WASHINGTON, DEPT CHEM, SEATTLE, WA 98195; UNIV WASHINGTON, DEPT BIOCHEM, SEATTLE, WA

98195;
ROCKEFELLER UNIV, NEW YORK, NY 10021. JOURNAL OF MOLECULAR RECOGNITION (MAR-APR 1997) Vol. 10, No. 2, pp. 93-100. Publisher: JOHN WILEY & SONS LTD. BAFFINS LANE CHICHESTER, W SUSSEX, ENGLAND PO19 1UD. ISSN:

0952-3499.

Pub. country: SWITZERLAND; USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Two human and twelve murine monoclonal antibodies directed against the main **bee venom** allergen phospholipase A(2) (PLA) were evaluated for their fine specificity of binding to antigen and their ability to inhibit the enzymatic activity of the antigen. Antibodies were induced by natural exposure of beekeepers to **bee venom** or immunization of mice via different methods. Both human monoclonal antibodies (hmAbs) were previously shown to recognize the native three-dimensional conformation of PLA and are directed against discontinuous epitopes which include lysine residue at position 25 as a contact residue. In contrast, six of the murine monoclonal antibodies (mmAbs) bind to the denatured structure of the protein as determined by enzyme-linked immunosorbent assay. The epitopes recognized are located near the C-terminal end (n=8), in the centre of the **polypeptide** (n=1), near the N-terminal end (n=1) or include the carbohydrate part (n=2) of the PLA molecule. The capacity of the antibodies to modify the enzymatic activity was also determined. The hmAbs significantly inhibit the enzyme (70-79%), whereas the mmAbs produced various degrees of inhibition (39-100%). Since the X-ray structure of PLA is known, the epitopes can be visualized in the context of the three-dimensional structure of the antigen. A qualitative correlation was found between the location of epitopes and the inhibition pattern. Strong inhibition was seen with those antibodies that recognize epitopes that lie on the surface

of the enzyme that is thought to contact the phospholipid bilayer. The results show that even though both hmAbs and most mmAbs inhibit the enzymatic activity of PLA, the antigen-binding properties of antibodies from different species raised after different routes of immunization differ significantly. Thus, detailed epitope mapping studies using murine antibodies prepared by artificial immunization may have limited value in predicting epitope patterns relevant to an antibody response to allergens in humans naturally exposed to antigen/**allergen**. (C)
1997 John Wiley & Sons, Ltd.

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L1 7518 S BEE VENOM
L2 502 S L1 AND POLYPEPTIDE
L3 76 S L2 AND PHOSPHOLIPASE A2
L4 4 S L3 AND HYALURONIDASE
L5 2 DUP REMOVE L4 (2 DUPLICATES REMOVED)
L6 1 S L2 AND ALLERGEN C

=> s l2 and mellitin

L7 8 L2 AND MELLITIN

=> dup remove l7

PROCESSING COMPLETED FOR L7

L8 8 DUP REMOVE L7 (0 DUPLICATES REMOVED)

=> d l8 1-8 cbib abs

L8 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2001 ACS
1991:401650 Document No. 115:1650 Effect of melittin on renin and
prostaglandin E2 release from rat renal cortical slices. Churchill, Paul
C.; Rossi, Noreen F.; Churchill, Monique C.; Ellis, Virginia R. (Sch.
Med., Wayne State Univ., Detroit, MI, 48201, USA). J. Physiol. (London),
428, 233-41 (English) 1990. CODEN: JPHYA7. ISSN: 0022-3751.

AB Expts. were designed to det. the effect of melittin on renin secretion.
Melittin is a **polypeptide** component of **bee**
venom which stimulates phospholipase A2 activity, thereby
increasing arachidonic acid release and prostaglandin (PG) synthesis, and
which inhibits protein kinase C activity. Either of these actions might
be expected to stimulate renin secretion, since renin secretion is
stimulated by arachidonic acid and by several PGs, and since renin
secretion is inhibited by several activators of protein kinase C. In rat
renal cortical slices incubated in a buffered and oxygenated physiol.
saline soln., 0.1-10 .mu.M melittin produced a concn.-dependent
stimulation of both PGE2 synthesis and renin secretion. However,
melittin-stimulated renin secretion is independent of melittin-stimulated
phospholipase A2 activity, arachidonic acid release, and PG synthesis,
since 10 .mu.M quinacrine (a phospholipase A2 antagonist) and 50 .mu.M
meclofenamate (a cyclooxygenase antagonist) antagonized basal and
melittin-stimulated PGE2 synthesis but had no effects on basal or
melittin-stimulated renin secretion. Melittin-stimulated renin secretion
was not produced by inhibition of protein kinase C. Ouabain partially
antagonized, but did not completely block, melittin-stimulated renin
secretion. Thus, melittin-stimulated phospholipase A2 activity probably
accounts for stimulated PGE2 prodn., but not for stimulated renin
secretion. The mechanism of melittin-stimulated renin secretion is
unclear; an effect on protein kinase C does not appear to be involved,

and
in contrast to the stimulatory effects of a variety of other substances,
melittin-stimulated renin secretion is only partially antagonized by
ouabain.

L8 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2001 ACS
1987:14911 Document No. 106:14911 Transient dichroism measurements of
rotational diffusion and interactions of proteins in erythrocyte

membranes. Cherry, Richard J. (Dep. Chem., Univ. Essex, Colchester/Essex, CO4 3SQ, UK). J. Chem. Soc., Faraday Trans. 2, 82(12), 2105-9 (English) 1986. CODEN: JCFTBS. ISSN: 0300-9238.

AB In human erythrocyte membranes the anion transport protein, band 3, may be

selectively labeled with eosin-5-maleimide. This has permitted a detailed study to be made of the rotational dynamics of band 3 by using the flash-induced transient dichroism method. In recent expts. the interaction of the **bee venom polypeptide**, melittin (I), with erythrocyte membranes was investigated. I caused a dramatic loss of rotational mobility of band 3, probably by electrostatic crosslinking of the protein into large relatively immobile aggregates. The concn. of I which produced this effect correlated with the concn. required for cell lysis. This suggests a possible role for I-protein interactions in the biol. activity of the **polypeptide**.

L8 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
1985:400131 Document No.: BA80:70123. MODE OF INHIBITORY ACTION OF MELITTIN ON

SODIUM POTASSIUM ATPASE ACTIVITY OF THE RAT SYNAPTIC MEMBRANE. CHEN C-C; LIN-SHIAU S-Y. PHARMACOLOGICAL INSTITUTE, COLLEGE OF MED., NATIONAL TAIWAN

UNIV., TAIPEI, TAIWAN 100.. BIOCHEM PHARMACOL, (1985) 34 (13), 2335-2342. CODEN: BCPA6. ISSN: 0006-2952. Language: English.

AB The effects of melittin from **bee venom**, cardiotoxin from Formosan cobra verom and ouabain on Na⁺-K⁺-ATPase activity of the synaptic membrane isolated from rat cerebral cortex were studied.

Melittin was the most potent in inhibiting Na⁺-K⁺-ATPase activity. Mg²⁺-ATPase was less susceptible than Na⁺-K⁺-ATPase to the inhibitory action of toxins. High K⁺ (30 mM) reversed the inhibitory action of **mellitin** on Na⁺-K⁺-ATPase but did not affect that of cardiotoxin. A comparison

between the effects of ouabain and melittin was studied, using double-reciprocal plots of Na⁺-K⁺-ATPase activity against K⁺. Both were competitive with K⁺ for binding to the K⁺ site. A median-effect plot revealed that ouabain

and melittin antagonized each other when inhibiting Na⁺-K⁺-ATPase. Phosphatidylcholine (PC) was the only one of the phospholipids tested capable of protecting Na⁺-K⁺-ATPase from the inhibitory action of

melittin but not that of ouabain. The inhibitory action of cardiotoxin on this enzyme was decreased by phosphatidylserine and sphingomyelin, in addition to PC. Evidently, melittin **polypeptide** potentially inhibits Na⁺-K⁺-ATPase, possibly by binding to the K⁺ site.

L8 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS
1980:617130 Document No. 93:217130 Effect of melittin-induced membrane alterations on rat heart adenylate cyclase activity. Lad, Pushkaraj L.; Shier, W. Thomas (Cell Biol. Lab., Salk Inst. Biol. Stud., San Diego, CA, 92138, USA). Arch. Biochem. Biophys., 204(2), 418-24 (English) 1980. CODEN: ABBIA4. ISSN: 0003-9861.

AB Melittin (I), a surface-active, 26-amino-acid **polypeptide** from **bee venom**, has been reported to alter a variety of membrane properties. I induced a biphasic alteration of rat heart microsomal adenylate cyclase (II) activity, stimulating it at low concn.

(<30 .mu.g/mL) and inhibiting it at higher concns. (.gtoreq.100 .mu.g/mL).
I potentiated NaF and 5'-guanylylimidodiphosphate activation of II below 40 .mu.g/mL, but it inhibited at high concns., except in the presence of high concns. of 5'-guanylylimidodiphosphate (10-4M). Basal and F--activated II exhibited no significant change in the Km for ATP in the presence of I <40 .mu.g/mL, but the V was elevated. Potentiation by I of II was obsd. at all concns. of F-, 5'-guanylylimidodiphosphate, and Mg2+ tested. The obsd. effects of I on rat heart II are consistent with its acting by altering the properties of membrane lipids with which the enzyme is assocd.

L8 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
1980:258876 Document No.: BA70:51372. HIGH RESOLUTION PROTON NMR STUDIES OF MONOMERIC MELITTIN IN AQUEOUS SOLUTION. LAUTERWEIN J; BROWN L R;
WUETHRICH

K. INST. CHIM. ORG., UNIV. LAUS., 2 RUE DE LA BARRE, LAUSANNE, SWITZ..
BIOCHIM BIOPHYS ACTA, (1980) 622 (2), 219-230. CODEN: BBACAQ. ISSN: 0006-3002. Language: English.
AB High resolution 1H-NMR at 360 MHz was used to characterize monomeric melittin [a **polypeptide** of 26 amino acids which composes 50% of the dry weight of **bee venom**] in aqueous solution. The monomeric form of **mellitin** prevailed at 3 mM concentration, pH 3.0 and temperatures between 30 and 90.degree. C, both in the absence of salt and with 6 M guanidium chloride. From comparison with model peptides and studies of the effects of 6 M guanidium chloride and variable temperature on the NMR parameters it was concluded that monomeric **mellitin** is predominantly in an extended flexible form, with the fragments 5-9 and 14-20 more highly structured than the rest of the amino acid sequence. The appearance of a 2nd, low abundant form of monomeric **mellitin**, which is in slow exchange on the NMR time scale with both the more abundant monomeric conformation and aggregated **mellitin**, was attributed to cis-trans isomerism of the peptide bond leu-13-pro-14.

L8 ANSWER 6 OF 8 MEDLINE
78137019 Document Number: 78137019. PubMed ID: 273232. Amino acid sequence of honeybee prepromelittin synthesized in vitro. Suchanek G; Kreil G; Hermodson M A. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

OF THE UNITED STATES OF AMERICA, (1978 Feb) 75 (2) 701-4. Journal code: PV3;

7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Translation of melittin messenger RNA from queen **bee venom** glands in a cell-free system from wheat germ yielded prepromelittin. Sequence analysis of the labeled in vitro product was performed by automatic Edman degradation of the intact **polypeptide** as well as by analysis of some of its proteolytic fragments. Prepromelittin was shown to be composed of 70 amino acids, two of which have not been identified. The sequence of melittin is located in the COOH-terminal third of the **polypeptide** chain (residues 44--69). Prepromelittin starts with a very hydrophobic pre-region, probably 21 residues long, followed by a pro-part of unusual sequence, containing

only alanine, proline, and acidic residues. At least three post-translational reactions are required to convert prepromelittin to **mellitin**.

L8 ANSWER 7 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
74184892 EMBASE Document No.: 1974184892. Hypersensitivity responses to
bee venom and to **mellitin**. Saelinger C.B.;
Higginbotham R.D.. Dept. Microbiol., Hlth Sci. Cent., Louisville, Ky.,
United States. International Archives of Allergy and Applied Immunology
46/1 (28-37) 1974.
CODEN: IAAAAM. Language: English.

AB **Bee venom** has both antigenic and anaphylactoid
properties. Immunization of mice with relatively small amounts of this
venom induced both cutaneous and fatal systemic hypersensitivity to
appropriate challenge with this material. Equivalent or greater systemic
hypersensitivity was also induced by adrenalectomy or by heat stress, and
thus a fatal reaction to this venom does not necessarily reflect an
allergic condition. All immune and anaphylactoid responses to **bee**
venom were reproduced with **mellitin**, a cationic
polypeptide constituent of this venom. In contrast, enhanced
response to phospholipase A was demonstrated only by systemic challenge

of
venom immunized mice. The results suggest that **mellitin** is an
important allergen as well as the major toxic constituent of whole
bee venom.

L8 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2001 ACS
1965:426213 Document No. 63:26213 Original Reference No. 63:4716f-h A new
method for the separation of the components of **bee venom**
, especially of the centrally active peptide, apamine. Habermann, E.;
Reiz, K. G. (Univ. Wuerzburg, Germany). Biochem. Z., 341(5), 451-66
(German) 1965.

AB From **bee venom** after gel filtration on Sephadex G-50,
hyaluronidase, phospholipase A, and the **polypeptide**
mellitin were obtained. Gel filtration (0.1M HCOONH₄, pH 4.5)
yields further 2 electrophoretically distinct peptides (FOa and FOp) and

a
fraction of the new basic peptide apamine, which by chromatography on
CM-cellulose (a 1:3 dild. soln.) and lyophilization was further purified
(2.3% of the total poison). Apamine produces specific, long lasting
excitation of the central nervous system in mice. Phospholipase A was
best prepd. (9-fold purification) by pH 6.9 gel filtration and subsequent
chromatography on Amberlite in 91% yield. Hyaluronidase was 40-fold
purified. Histamine was the only low-mol.-wt. pharmacol. active
component.

=> s 12 and adoplain

L9 0 L2 AND ADOPLAIN

=> s 12 and adolapin

L10 14 L2 AND ADOLAPIN

=> dup remove l10

PROCESSING COMPLETED FOR L10

L11 7 DUP REMOVE L10 (7 DUPLICATES REMOVED)

=> d l11 1-7 cbib abs

L11 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS
1987:95798 Document No. 106:95798 **Bee venom**

adolapin: effect on thromboxane A2 and prostacyclin plasma levels in rats with model acute inflammation. Shkenderov, S.; Koburova, K.; Chavdarova, V. (State Inst. Control Drugs, Sofia, 1000, Bulg.). Dokl. Bolg. Akad. Nauk, 39(9), 155-7 (English) 1986. CODEN: DBANAD. ISSN: 0366-8681.

AB In rats, **adolapin** (a basic **polypeptide** from **bee venom**) [79029-92-8] (20 .mu.g/kg, s.c.) did not affect the normal blood plasma levels of prostacyclin [35121-78-9] and thromboxane A3 [60114-68-3], but did antagonize the increases in the formation of these compds. in the blood plasma induced by induction of inflammation by injection of carrageenin into the right hind foot pad. **Adolapin** also inhibited cyclooxygenase [39391-18-9] in vitro, but its max. effect was 60-80%. Thus, **adolapin** may have therapeutic effects without causing disturbances of the physiol. balance of the prostaglandin-forming system.

L11 ANSWER 2 OF 7 MEDLINE
86022057 Document Number: 86022057. PubMed ID: 2996298. Further
investigation on the antiinflammatory properties of **adolapin**--

bee venom polypeptide. Koburova K L; Michailova S G; Shkenderov S V. ACTA PHYSIOLOGICA ET PHARMACOLOGICA BULGARICA, (1985) 11 (2) 50-5. Journal code: 1SL; 7512568. ISSN: 0323-9950. Pub. country: Bulgaria. Language: English.

AB **Adolapin** is a basic **polypeptide** (M. W. 11500) isolated from **bee venom**. It showed marked antiinflammatory and analgetic properties and inhibited cyclooxygenase. It was found that **adolapin** inhibited also the activity of **bee venom** phospholipase A2 (7 nmole/ml producing about 80% inhibition of 2.5 nmole/ml phospholipase). In addition it inhibited the lipoxigenase from human platelets (4.5 nmole/ml inhibited about 80% of the activity of 0.8 mg protein/ml). **Adolapin** (20 micrograms/kg) caused an elevation of c-GMP level in rat spleen and brain as well as a decrease of c-AMP in rat spleen. **Adolapin** was tested by the "tail flick" method which allowed the demonstration of its analgetic action. The partial inhibition of the analgetic effect of **adolapin** induced by naloxon, proved the participation of a central mechanism of action. Similar to other nonsteroid analgetics, **adolapin** displayed antipyretic effect (40 micrograms/kg caused an inhibition of the mean temperature rise about 62%).

L11 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS
1985:540101 Document No. 103:140101 **Adolapin** effect on histamine

release by rat peritoneal mastocytes. Mikhailova, S.; Koburova, K.; Shkenderov, S. (Bulg.). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 18, 39-43 (Bulgarian) 1985. CODEN: IDISD4. ISSN: 0323-9438.

AB The effect of **adolapin**, a basic **polypeptide** of **bees venom** with mol. wt. 11,500, on histamine release by peritoneal mastocytes of rats was investigated. Histamine concn. was detd. by a modification of the spectrofluorometric method. At concn. ranging from 0.1 mcg/mL to 200 mcg/mL **adolapin** caused no histamine release whatsoever. At concns. ranging from 1 mcg/mL to 20 mcg/mL, there was up to 60% inhibition of histamine release, provoked by compd. 48/80 (0.3 mcg/mL). The effect of the calcium ionophore A23187 (0.3 mcg/mL) was not influenced by the **polypeptide** concns. tested. The possible relationship between **adolapin**-induced

inhibition of histamine release and its effect on the metab. of arachidonic acid is discussed.

L11 ANSWER 4 OF 7 MEDLINE
85101057 Document Number: 85101057. PubMed ID: 6440766. [Antipyretic effect of a **polypeptide** from **bee venom**--**adolapin**]. Antipiretichen efekt na edin polipeptid ot pchelnata otrova--**adolapin**. Koburova K; Mikhailova S; Shkenderov S. EKSPERIMENTALNA MEDITSINA I MORFOLOGIJA, (1984) 23 (3) 143-8. Journal code: EEB; 0007506. ISSN: 0367-0643. Pub. country: Bulgaria. Language: Bulgarian.

L11 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
1984:1839 Document No. 100:1839 Anaphylactogenic and antigenic properties of

adolapin, a **polypeptide** isolated from **bee venom**. Koburova, K.; Grigorova, K.; Shkenderov, S.; Gencheva, G. (Bulg.). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 16, 95-9 (Bulgarian) 1983. CODEN: IDISD4. ISSN: 0323-9438.
AB Double radial immunodiffusion in agar gel demonstrated that during prolonged immunization of rabbits, **adolapin** [79029-92-8] fails to produce pptg. antibodies. **Adolapin** proves to be a weak anaphylactogen since anaphylactic reactions are obsd. in guinea pigs at doses exceeding as much as 125 times the therapeutic one.

L11 ANSWER 6 OF 7 MEDLINE
82200186 Document Number: 82200186. PubMed ID: 7080045. **Adolapin**--a newly isolated analgetic and anti-inflammatory **polypeptide** from **bee venom**. Shkenderov S; Koburova K. TOXICON, (1982) 20 (1) 317-21. Journal code: VWT; 1307333. ISSN: 0041-0101. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Adolapin** was isolated by a two-step procedure: gel filtration and chromatography on CM cellulose. The molecular mass of the **polypeptide** as determined by SDS electrophoresis and amino acid composition proved to be 11500 and 11092 respectively. **Adolapin** exhibited a potent analgesic effect demonstrated by the "writhing" test (ED50-0,016mg/kg) and by the Randall-Sellito's test (ED50-0,013 mg/kg). The anti-inflammatory activity of **adolapin** was most marked with regard to carrageenin, prostaglandin and adjuvant rat hind paw edemas and adjuvant polyarthritis. The **adolapin** effects are presumably due to its capacity to inhibit the prostaglandin synthase system, following a biphasic dose-response relationship. It is likely that central mechanisms are also involved in the analgetic action of **adolapin**.

L11 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2001 ACS
1981:561805 Document No. 95:161805 Lipoxxygenase inhibiting activity of **adolapin** - an antiinflammatory **polypeptide** from **bee venom**. Koburova, K.; Shkenderov, S. (USSR). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 14, 51-4 (Bulgarian) 1981. CODEN: IDISD4.

AB **Adolapin** [79029-92-8], a peptide from **bee venom** with antiinflammatory activity, inhibits lipoxxygenase [9029-60-1]. The max. effect (42% inhibition) is obtained after 15 min preincubation of 2 .times. 10-6M **adolapin** with the enzyme.

=> s 12 and minimise

L12 4 L2 AND MINIMINE

=> dup remove l12

PROCESSING COMPLETED FOR L12

L13 2 DUP REMOVE L12 (2 DUPLICATES REMOVED)

=> d l13 1-2 chib abs

L13 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
1997:118167 Document No.: PREV199799417370. Chromatographic and membrane
purification of **polypeptide** compounds from honey **bee**
venom. Klyushnichenko, V. E. (1); Syagailo, Ya. V.. (1) Shemyakin
and Ovchinnikov Inst. Bioorganic Chem., Russia Acad. Sci., Ul.
Miklukho-Maklaya 16/10, 117871 GSP Moscow V-437 Russia. Journal of

Natural
Toxins, (1997) Vol. 6, No. 1, pp. 111-119. ISSN: 1058-8108. Language:
English.

AB The compounds of venom *Apis mellifera* contains a set of
polypeptides: melittin, phospholipase A2, apamin, MCD-peptide,
minimine, and other substances. The traditional schemes of
purification of honey **bee venom** earlier included
different types of chromatography. The present work proposes the
combination of chromatographic and membrane methods for purification of
honey **bee venom**. The main advantage of membrane
purification is that melittin in water exists as a monomer (2.7 kD) but
at high salt concentration as a tetramer. Phospholipase A2 may exist as a
monomer (15.4 kD) and a dimer similar to melittin. The purification
scheme covers: alcohol sedimentation, separation of melittin from the rest of
phospholipase A2 by means of membranes with exclusion limit of 15 and 5
kD, ion exchange and scale up RP HPLC of melittin. Each step of
purification was analyzed by RP HPLC. The purity of the final product
under different chromatographic conditions was compared. The melittin was
purified from the impurities more than 98% by RP HPLC.

L13 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
72049998 Document Number: 72049998. PubMed ID: 5001226.
Polypeptides minimine and melittin from **bee**
venom: effects on *Drosophila*. Lowy P H; Sarmiento L; Mitchell H K.
ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1971 Jul) 145 (1) 338-43.
Journal code: 6SK; 0372430. ISSN: 0003-9861. Pub. country: United States.
Language: English.

=> s l2 and acid phosphatase

4 FILES SEARCHED...

L14 0 L2 AND ACID PHOSPHATASE

=> s l2 and protease inhibitor

L15 1 L2 AND PROTEASE INHIBITOR

=> d l15 chib abs

L15 ANSWER 1 OF 1 MEDLINE
84261515 Document Number: 84261515. PubMed ID: 6086337. Molecular
properties of the apamin-binding component of the Ca²⁺-dependent K⁺
channel. Radiation-inactivation, affinity labelling and solubilization.
Schmid-Antomarchi H; Hugues M; Norman R; Ellory C; Borsotto M; Lazdunski
M. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1984 Jul 2) 142 (1) 1-6. Journal
code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST:

Germany,

Federal Republic of. Language: English.

AB Radiation-inactivation was used to assess the functional size of the
apamin-binding component of the Ca²⁺-dependent K⁺ channel. The amount of
specific binding of 125I-apamin to receptors in synaptic membranes of rat
cortex decayed exponentially with increasing doses of ionizing radiation
and target size analysis was consistent with a relative molecular mass of
250 000 +/- 20 000 for the 125I-apamin receptor. Analysis on sodium
dodecyl sulfate gels following covalent cross-linking of 125I-apamin to
its receptor in a synaptosomal membrane preparation from rat cortex
revealed a single labelled **polypeptide** chain of Mr = 33 000 +/-
2000 in the presence of **protease inhibitors**. Our
results suggest that the Ca²⁺-dependent K⁺ channel from rat cortex is an
oligomeric structure of Mr = 250 000 +/- 20 000 containing an
apamin-binding subunit of Mr = 33 000 +/- 2000. The apamin-binding
component of the Ca²⁺-dependent K⁺ channel from rat synaptosomes was
solubilized using detergents such as sodium cholate or
3-[(3-cholamidopropyl)dimethylammonio]-1-propane sulfonate. Phospholipids
did not increase the stability of the apamin-binding component during the
solubilization. Binding of apamin to its solubilized receptor is
reversible and saturable. The dissociation constant of the

apamin-receptor

complex is 40-150 pM, the rates constants of association and dissociation
being 3.2 X 10⁽⁶⁾ M⁻¹s⁻¹ and 1.4 X 10⁽⁻⁴⁾s⁻¹ respectively. These binding
characteristics are similar to those found for the membrane-bound apamin
receptor.

=> s 12 and glycosyated IgE binding protein

2 FILES SEARCHED...

L16 0 L2 AND GLYCOSYATED IGE BINDING PROTEIN

=> d his

(FILE 'HOME' ENTERED AT 15:52:23 ON 16 JUL 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 15:52:41 ON
16 JUL 2001

L1 7518 S BEE VENOM
L2 502 S L1 AND POLYPEPTIDE
L3 76 S L2 AND PHOSPHOLIPASE A2
L4 4 S L3 AND HYALURONIDASE
L5 2 DUP REMOVE L4 (2 DUPLICATES REMOVED)
L6 1 S L2 AND ALLERGEN C
L7 8 S L2 AND MELLITIN
L8 8 DUP REMOVE L7 (0 DUPLICATES REMOVED)
L9 0 S L2 AND ADOPLAIN
L10 14 S L2 AND ADOLAPIN

L11 7 DUP REMOVE L10 (7 DUPLICATES REMOVED)
 L12 4 S L2 AND MINIMINE
 L13 2 DUP REMOVE L12 (2 DUPLICATES REMOVED)
 L14 0 S L2 AND ACID PHOSPHATASE
 L15 1 S L2 AND PROTEASE INHIBITOR
 L16 0 S L2 AND GLYCOSYATED IGE BINDING PROTEIN

=> s k3 and analog

L17 552 K3 AND ANALOG

=> s l3 and and analog

MISSING TERM 'AND AND'
 The search profile that was entered contains a logical operator followed immediately by another operator.

=> s l3 and analog

L18 0 L3 AND ANALOG

=>

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=>

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=> LOG Y

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 PASSWORD:
 TERMINAL (ENTER 1, 2, 3, OR ?):2

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 NEWS 3 Feb 06 Engineering Information Encompass files have new names
 NEWS 4 Feb 16 TOXLINE no longer being updated

NEWS 5 Apr 23 Search Derwent WPINDEX by chemical structure
 NEWS 6 Apr 23 PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS 7 May 07 DGENE Reload
 NEWS 8 Jun 20 Published patent applications (A1) are now in USPATFULL
 NEWS 9 JUL 13 New SDI alert frequency now available in Derwent's
 DWPI and DPCI

NEWS EXPRESS July 11 CURRENT WINDOWS VERSION IS V6.0b,
 CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP),
 AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2001
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 NEWS INTER General Internet Information
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 NEWS PHONE Direct Dial and Telecommunication Network Access to STN
 NEWS WWW CAS World Wide Web Site (general information)

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=> s peptide immunotherapy

L1 189 PEPTIDE IMMUNOTHERAPY

=> s 11 and bee venom

L2 30 L1 AND BEE VENOM

=> dup remove 12

PROCESSING COMPLETED FOR L2

L3 14 DUP REMOVE L2 (16 DUPLICATES REMOVED)

=> d 13 1-14 cbib abs

L3 ANSWER 1 OF 14 MEDLINE DUPLICATE 1
2001262363 Document Number: 21203275. PubMed ID: 11306962. Mechanism of
IL-10-induced T cell inactivation in allergic inflammation and normal
response to allergens. Akdis C A; Joss A; Akdis M; Blaser K. (Swiss
Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland..
akdism@siaf.unizh.ch) . INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY,
(2001 Jan-Mar) 124 (1-3) 180-2. Ref: 14. Journal code: BJ7; 9211652.
ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB BACKGROUND: Induction of specific unresponsiveness (tolerance/anergy) in
peripheral T cells and recovery by cytokines from the tissue
microenvironment represent two key steps in specific immunotherapy (SIT)
with whole allergen or antigenic T cell peptides. METHODS:
Antigen-specific T cell responses and molecular mechanisms of T cell
inactivation were investigated during conventional SIT, T cell epitope
peptide immunotherapy and natural exposure to
bee venom in allergic and hyperimmune individuals.
RESULTS: T cell unresponsiveness, initiated by autocrine action of IL-10,
is characterized by suppressed proliferative and cytokine responses. The
unresponsive T cells can be reactivated by different cytokines that may
mimic the microenvironmental cytokine influence. IL-10 initiates
peripheral tolerance by blocking the CD28 costimulatory signal in T
cells.

Coprecipitation experiments reveal that upon stimulation CD28 and IL-10
receptor are physically associated in T cells. Accordingly, IL-10 binding
to its receptor inhibits CD28 tyrosine phosphorylation, the initial step
of the CD28 signaling pathway. This leads to inhibition of
phosphatidylinositol 3-kinase p85 binding to CD28. IL-10 only affects T
cells that receive a stimulation with low numbers of triggered T cell
receptors and that require costimulatory signals by CD28. CONCLUSION:
These data demonstrate the pivotal role of autocrine IL-10 and the
interaction of its receptor with CD28 in the induction of T cell
tolerance

as an immunoregulatory mechanism controlling antigen-specific T cell
responses. Copyright 2001 S. Karger AG, Basel

L3 ANSWER 2 OF 14 MEDLINE DUPLICATE 2
2000386468 Document Number: 20354865. PubMed ID: 10898500.
Allergen-derived long **peptide immunotherapy**
down-regulates specific IgE response and protects from anaphylaxis. von
Garnier C; Astori M; Kettner A; Dufour N; Heusser C; Corradin G; Spertini
F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire
Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000
Jun) 30 (6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub.
country: GERMANY: Germany, Federal Republic of. Language: English.
AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J
mice were sensitized with low dose alum-adsorbed phospholipase A2 (PLA2),

a major **bee venom** allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides (44- to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long peptide mixture were fully protected from anaphylaxis. This indicated that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L3 ANSWER 3 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
 2000:192482 The Genuine Article (R) Number: 287WR. Allergen **peptide immunotherapy**: Results of a safety and immunogenicity trial with phospholipase A2 derived long peptides in **bee venom** hypersensitive patients. Spertini F (Reprint); Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin G. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS,

MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L3 ANSWER 4 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
 2000:58615 The Genuine Article (R) Number: 273LF. Modulation of Th2 responses by peptide analogues in a murine model of allergic asthma: Amelioration or deterioration of the disease process depends on the Th1 or Th2 skewing characteristics of the therapeutic peptide. Janssen E M; vanOosterhout A J M; vanRensen A J M L; vanEden W; Nijkamp F P; Wauben M H M (Reprint). UNIV UTRECHT, FAC VET MED, DEPT IMMUNOL, INST INFECT DIS & IMMUNOL, POB 80165, NL-3508 TD UTRECHT, NETHERLANDS (Reprint); UNIV UTRECHT, FAC VET MED, DEPT IMMUNOL, INST INFECT DIS & IMMUNOL, NL-3508 TD UTRECHT, NETHERLANDS; UNIV UTRECHT, FAC PHARM, DEPT PHARMACOL & PATHOPHYSIOL, NL-3508 TD UTRECHT, NETHERLANDS; UNIV UTRECHT, FAC PHARM, DEPT PHARMACEUT, NL-3508 TD UTRECHT, NETHERLANDS. JOURNAL OF IMMUNOLOGY (15 JAN 2000) Vol. 164, No. 2, pp. 580-588. Publisher: AMER ASSOC IMMUNOLOGISTS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0022-1767. Pub. country: NETHERLANDS. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
 AB Allergen-specific CD4(+) Th2 cells play an important role in the immunological processes of allergic asthma. Previously we have shown that, by using the immunodominant epitope OVA(323-339), **peptide immunotherapy** in a murine model of OVA induced allergic asthma, stimulated OVA-specific Th2 cells, and deteriorated airway hyperresponsiveness and eosinophilia. In the present study, we defined

four modulatory peptide analogues of OVA(323-339) with comparable MHC class II binding affinity, These peptide analogues were used for immunotherapy by s.c. injection in OVA-sensitized mice before OVA challenge, Compared with vehicle-treated mice, treatment with the Th2-skewing mild-type peptide and a Th2-skewing partial agonistic peptide (335N-A) dramatically increased airway eosinophilia upon OVA challenge,

In contrast, treatment with a Th1-skewing peptide analogue (336E-A) resulted in a significant decrease in airway eosinophilia and OVA-specific IL-4

and IL-5 production, Our data show for the first time that a Th1-skewing peptide analogue of a dominant allergen epitope can modulate allergen-specific Th2 effector cells in an allergic response in vivo, Furthermore, these data suggest that the use of Th1-skewing peptides instead of wild-type peptide may improve **peptide immunotherapy** and may contribute to the development of a successful and safe immunotherapy for allergic patients.

L3 ANSWER 5 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen **peptide immunotherapy**: Results of a safety and immunogenicity trial with phospholipase A2-derived long peptides in **bee venom** hypersensitive patients. Spertini, Francois (1); Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1) Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy

and Clinical Immunology., (Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary Language: English.

L3 ANSWER 6 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:308471 The Genuine Article (R) Number: 304VV. Specific **peptide immunotherapy**. Akdis C A (Reprint); Blaser K. SWISS INST ALLERGY & ASTHMA RES, OBERE STR 22, CH-7270 DAVOS, SWITZERLAND (Reprint). REVUE FRANCAISE D ALLERGOLOGIE ET D IMMUNOLOGIE CLINIQUE (APR 2000) Vol. 40,

No. 3, pp. 309-317. Publisher: EXPANSION SCI FRANCAISE. 31 BLVD LATOUR MAUBOURG, 75007 PARIS, FRANCE. ISSN: 0335-7457. Pub. country: SWITZERLAND. Language: English.

L3 ANSWER 7 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:705152 The Genuine Article (R) Number: 353MP. Peptide-mediated immune responses in specific immunotherapy. Haselden B M; Kay A B; Larche M (Reprint). NATL HEART & LUNG INST, IMPERIAL COLL, SCH MED, DOVEHOUSE ST, LONDON SW3 6LY, ENGLAND (Reprint); NATL HEART & LUNG INST, IMPERIAL COLL, SCH MED, LONDON SW3 6LY, ENGLAND. INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY (AUG 2000) Vol. 122, No. 4, pp. 229-237. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1018-2438. Pub. country: ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Conventional immunotherapy using whole allergen extracts has been shown to be an effective, disease-modifying treatment in carefully selected

patients with allergic conjunctivo-rhinitis, asthma and bee and wasp venom hypersensitivity. However, this form of therapy is associated with the risk of systemic anaphylaxis, which, when severe, can be life threatening.

A potentially significant reduction in the incidence of IgE-mediated events during immunotherapy may be achieved by the use of short peptides corresponding to T cell epitopes which, by virtue of their size, are incapable of cross-linking allergen-specific IgE bound to the surface of mast cells and basophils. Initial clinical studies have demonstrated degrees of efficacy which have, in some cases, been associated with adverse events occurring immediately or several hours after peptide administration. Preliminary data from studies employing shorter peptides (20 amino acids or less) suggest that improved efficacy may be achieved by using peptides of defined major histocompatibility complex-binding specificity administered in an incremental dose fashion comparable to conventional immunotherapy. This review will discuss the concept of **peptide immunotherapy** and the implications of recent studies, Copyright (C) 2000 S. Karger AG, Basel.

L3 ANSWER 8 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:757120 The Genuine Article (R) Number: 241UT. **Peptide immunotherapy**. Muller U R (Reprint). ZIEGLERSPITAL BERN, MED KLIN, MORILLONSTR 75-91, CH-3001 BERN, SWITZERLAND (Reprint). ALLERGY (OCT 1999) Vol. 54, Supp. [56], pp. 45-46. Publisher: MUNKSGAARD INT PUBL LTD.
35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0105-4538
. Pub. country: SWITZERLAND. Language: English.

L3 ANSWER 9 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:559025 The Genuine Article (R) Number: 215RZ. Opposite effects of immunotherapy with ovalbumin and the immunodominant T-cell epitope on airway eosinophilia and hyperresponsiveness in a murine model of allergic asthma. Janssen E M; Wauben M H M; Jonker E H; Hofman G; VanEden W; Nijkamp F P; vanOosterhout A J M (Reprint). UNIV UTRECHT, FAC PHARM, DEPT PHARMACOL & PATHOPHYSIOL, POB 80-082, NL-3508 TB UTRECHT, NETHERLANDS (Reprint); UNIV UTRECHT, FAC PHARM, DEPT PHARMACOL & PATHOPHYSIOL, NL-3508 TB UTRECHT, NETHERLANDS; UNIV UTRECHT, FAC MED VET, DEPT IMMUNOL, INST INFECT DIS & IMMUNOL, NL-3508 TB UTRECHT, NETHERLANDS. AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY (JUL 1999) Vol. 21, No. 1, pp. 21-29. Publisher: AMER LUNG ASSOC. 1740 BROADWAY, NEW YORK, NY 10019. ISSN: 1044-1549. Pub. country: NETHERLANDS. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB In the present study, we investigated immunotherapy using an entire protein or an immunodominant epitope in a murine model of allergic asthma.

Immunotherapy was performed in ovalbumin (OVA)-sensitized mice before OVA challenge. Mice were treated subcutaneously with OVA, the immunodominant epitope OVA(323-339), Or vehicle. In vehicle-treated animals, repeated OVA challenge induced increased serum levels of OVA-specific immunoglobulin (Ig)G1, IgE, airway eosinophilia, and hyperresponsiveness, compared with saline-challenged animals. In addition, interleukin (IL)-4 and IL-5

production upon OVA restimulation of lung-draining lymph node cells in vitro were significantly increased in OVA-challenged animals. Immunotherapy using OVA significantly reduced airway eosinophilia and hyperresponsiveness. This finding was accompanied by significantly

reduced

OVA-specific IL-4 and IL-5 production. Further, OVA immunotherapy induced increased serum levels of OVA-specific IgG1, whereas OVA-specific IgG2a and IgE levels were not affected. In contrast to OVA immunotherapy, immunotherapy with OVA323-339 aggravated airway eosinophilia and hyperresponsiveness. OVA-specific IgG1, IgG2a, and IgG serum levels, and in vitro IL-4 and IL-5 production, were not affected. Thus, immunotherapy with protein resulted in beneficial effects on airway eosinophilia and hyperresponsiveness, which coincided with a local reduced T-helper 2

(Th2)

response. In contrast, **peptide immunotherapy** aggravated airway hyperresponsiveness and eosinophilia, indicating a

local

enhanced Th2 response.

L3 ANSWER 10 OF 14 MEDLINE DUPLICATE 3
1998311035 Document Number: 98311035. PubMed ID: 9648701. Successful immunotherapy with T-cell epitope peptides of **bee venom** phospholipase A2 induces specific T-cell anergy in patients allergic to **bee venom**. Muller U; Akdis C A; Fricker M; Akdis M; Blesken T; Bettens F; Blaser K. (Medical Division, Zieglerspital, Bern, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1998 Jun) 101 (6 Pt 1) 747-54. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Specific immunotherapy with honeybee venom (BV) is highly effective, but allergic side effects can occur during treatment. Immunotherapy with peptides containing major T-cell epitopes of the relevant allergen or allergens provides an alternative strategy without these problems. OBJECTIVE: The study investigates the immunologic mechanisms and clinical effects of immunotherapy with T-cell epitope peptides of the major BV allergen, the phospholipase A2 (PLA). METHODS: Five patients with IgE-mediated systemic allergic reactions to bee stings were treated with a mixture of three T-cell epitope peptides of PLA. Ten patients allergic to BV receiving whole BV immunotherapy served as control

subjects. Increasing doses of the peptide mixture, up to a maintenance dose of 100 microg, were administered subcutaneously within 2 months. The patients were then challenged with PLA and 1 week later with a bee sting. The cellular and humoral immune response was measured in vitro. RESULTS: No allergic side effects were caused by the **peptide immunotherapy**, and all patients tolerated the challenge with PLA without systemic allergic symptoms. Two patients developed mild systemic allergic reactions after the bee sting challenge. After **peptide immunotherapy**, specific proliferative responses to PLA and the peptides in peripheral blood mononuclear cells were decreased in successfully treated patients. The production of TH2 and TH1 cytokines

was

inhibited, and B cells were not affected in their capacity to produce specific IgE and IgG4 antibodies. Their levels increased after allergen challenge in favor of IgG4. CONCLUSIONS: Immunotherapy of BV allergy with short T-cell peptides of PLA induces epitope-specific anergy in

peripheral

T cells and changes the specific isotype ratio in a fashion similar to that of conventional immunotherapy in successfully treated patients.

L3 ANSWER 11 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
1998:828329 The Genuine Article (R) Number: 131XK. Immunotherapy with Fel d

1

peptides decreases IL-4 release by peripheral blood T cells of patients allergic to cats. Pene J (Reprint); Desroches A; Paradis L; Lebel B; Farce M; Nicodemus C F; Yssel H; Bousquet J. HOP ARNAUD VILLENEUVE,

INSERM

U454, 375 AVE DU DOYEN G GIRAUD, F-34295 MONTPELLIER 5, FRANCE (Reprint); HOP ARNAUD VILLENEUVE, CLIN MALAD RESPIRATOIRES, F-34295 MONTPELLIER 5, FRANCE; IMMULOGIC, WALTHAM, MA. JOURNAL OF ALLERGY AND CLINICAL

IMMUNOLOGY

(OCT 1998) Vol. 102, No. 4, Part 1, pp. 571-578. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: FRANCE; USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB

Background: Cells producing a T-H2-cytokine profile play an important role in the onset and maintenance of atopic diseases, and therefore specific immunotherapy is aimed to induce a switch to cells producing a T-H1- or T-H0-cytokine profile. Recently, a novel form of immunotherapy making use of synthetic peptides from the major cat allergen Fel d 1 has been developed, but its mechanisms of action are unknown.

Objectives: We examined the effects of immunotherapy with Fel d1 peptides on the response to bronchial provocation tests (PD20FEV1) with a standardized Fel d 1 cat extract on Fel d 1-specific serum IgE and IgG Levels and in vitro IL-4 and IFN-gamma production.

Methods: Patients allergic to cats received 6 weekly injections of 7.5 mu g (Low dose), 75 mu g (medium dose), or 750 mu g (high dose) of Fel d

1

peptides (25 patients) or a placebo (6 patients). Results: Six weeks

after

ending immunotherapy, posttreatment PD20FEV1 was not significantly different between the treated and placebo groups. However, in the medium- and high-dose groups there was a significant improvement between baseline and posttreatment days. IL-4 release was significantly reduced in the

high

dose-treated group ($P < .005$, Wilcoxon W test), whereas it was unchanged in the low or medium dose- and in the placebo-treated groups. In all groups, IFN-gamma, IgE, and IgG levels remained unchanged.

Conclusion: There was no correlation between the improvement of PD20FEV1 and the decrease in IL-4 production. These data suggest that **peptide immunotherapy** may act by shifting, the Fel d 1-induced response of PBMCs in vitro from the T-H2-like to the T-H0-like phenotype.

L3 ANSWER 12 OF 14 MEDLINE

DUPLICATE 4

97400299 Document Number: 97400299. PubMed ID: 9257793. Modulation of T-cell response to phospholipase A2 and phospholipase A2-derived peptides by conventional **bee venom** immunotherapy. Kammerer R; Chvatchko Y; Kettner A; Dufour N; Corradin G; Spertini F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY,

(1997

Jul) 100 (1) 96-103. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Immunologic mechanisms of desensitization are still incompletely understood. Safer methods of immunotherapy with reduced

risks

of anaphylaxis need to be developed. OBJECTIVE: To study the effects of conventional venom immunotherapy (VIT) on phospholipase A2 (PLA2)-specific T cells and on T-cell reactivity to short and long synthetic peptides that

map the PLA2 molecule. METHOD: Proliferation of a CD4+ cell-enriched peripheral blood mononuclear cell fraction and cytokine secretion by T cell lines from patients hypersensitive to **bee venom** and undergoing VIT in response to PLA2 and PLA2 synthetic peptides were measured. RESULTS: T-cell proliferation in response to three synthetic peptides, 40 to 60 amino acids long and mapping the entire PLA2 molecule with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to 134)

steadily increased during the first 14 weeks of VIT corresponding to the treatment period with incremental doses of antigen. These results are in contrast

to the low proliferation indices obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the molecule with short peptides. At the end of VIT (after 3 to 5 years), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by

a shift in the pattern of cytokine secretion by T cell lines from a T(H0)-type to a T(H1)-type pattern. CONCLUSION: After a transient

increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of cytokine secretion from a T(H0)-type to a T(H1)-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 molecule appear to be efficient T cell stimulators and may represent potential candidates for **peptide immunotherapy**.

L3 ANSWER 13 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
97220357 EMBASE Document No.: 1997220357. [Immunotherapy with T cell peptides

of **bee venom** phospholipase A2]. IMMUNOTHERAPIE MIT T-ZELL-PEPTIDEN DER BIENENGIFT-PHOSPHOLIPASE A2. Muller U.R.; Akdis C.A.; Fricker M.; Blaser K.. Prof. Dr. U.R. Muller, Zieglerspital, Medizinische Klinik, CH-3007 Bern, Switzerland. Allergo Journal 6/SUPPL. 1 (S53-S54) 1997.

Refs: 6.

ISSN: 0941-8849. CODEN: ALJOEY. Pub. Country: Germany. Language: German. Summary Language: German; English.

AB 5 patients with a history of bee sting allergy and strongly positive skin tests as well as high titers of **bee venom** and phospholipase A2-specific IgE serum antibodies underwent immunotherapy with an equimolar mixture of three T cell peptides of the major **bee venom** allergen phospholipase A2. A cumulative dose of around 40 .mu.g of the peptide mixture was applied. All patients tolerated a first provocation test with native phospholipase A2 without systemic allergic symptoms, while 2 showed mild symptoms following a

sting provocation test. In vitro studies suggest induction of allergen-specific T cell anergy by **peptide immunotherapy**.

L3 ANSWER 14 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310225 Document No.: PREV199699032581. T cell epitope mapping with short or long synthetic peptides. Kettner, A. (1); Chvatachko, Y.; Kammerer, R.;

Dufour, N.; Corradin, G. (1); Spertini, F.. (1) Inst. Biochem., 1066
Epalinges Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp. A1479.
Meeting Info.: Joint Meeting of the American Society for Biochemistry and
Molecular Biology, the American Society for Investigative Pathology and
the American Association of Immunologists New Orleans, Louisiana, USA

June

2-6, 1996 ISSN: 0892-6638. Language: English.

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(FILE 'HOME' ENTERED AT 12:21:09 ON 23 JUL 2001)

FILE 'MEDLINE, EMBASE, SCISEARCH, BIOSIS, CAPLUS' ENTERED AT 12:21:22 ON
23 JUL 2001

L1 189 S PEPTIDE IMMUNOTHERAPY
L2 30 S L1 AND BEE VENOM
L3 14 DUP REMOVE L2 (16 DUPLICATES REMOVED)

=> s l1 and phospholipase A2

L4 19 L1 AND PHOSPHOLIPASE A2

=> dup remove l4

PROCESSING COMPLETED FOR L4

L5 8 DUP REMOVE L4 (11 DUPLICATES REMOVED)

=> d l5 1-8 cbib abs

L5 ANSWER 1 OF 8 MEDLINE DUPLICATE 1
2000386468 Document Number: 20354865. PubMed ID: 10898500.

Allergen-derived long **peptide immunotherapy**
down-regulates specific IgE response and protects from anaphylaxis. von
Garnier C; Astori M; Kettner A; Dufour N; Heusser C; Corradin G; Spertini
F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire
Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000
Jun) 30 (6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub.
country: GERMANY: Germany, Federal Republic of. Language: English.

AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J
mice were sensitized with low dose alum-adsorbed **phospholipase**
A2 (PLA2), a major bee venom allergen. Presensitized mice were
treated by daily i.p. injections of a mixture of three long overlapping
peptides (44- to 60-mer) spanning the entire PLA2 molecule (100
microg/peptide) for 6 consecutive days. This therapeutic approach induced
a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a
marked T cell hyporesponsiveness. T cell cytokine secretion was
characterized by a shift from a Th2 to a Th1 profile. Prophylactic
treatment of naive mice with long peptides prior to sensitization with
PLA2 induced a comparable modulation of B and T cell responses. Upon i.p.
challenge with native PLA2, presensitized mice treated with the long
peptide mixture were fully protected from anaphylaxis. This indicated

that
allergen-derived long overlapping peptides were safe and able to modulate
an established Th2 response or to prevent its development. Furthermore,
long peptide-based immunotherapy provided clinical protection against

anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L5 ANSWER 2 OF 8 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:192482 The Genuine Article (R) Number: 287WR. Allergen **peptide immunotherapy**: Results of a safety and immunogenicity trial with **phospholipase A2** derived long peptides in bee venom hypersensitive patients. Spertini F (Reprint); Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin G. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO

63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L5 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen **peptide immunotherapy**: Results of a safety and immunogenicity trial with **phospholipase A2**-derived long peptides in bee venom hypersensitive patients. Spertini, Francois (1); Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1) Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy

and Clinical Immunology., (Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary Language: English.

L5 ANSWER 4 OF 8 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:308471 The Genuine Article (R) Number: 304VV. Specific **peptide immunotherapy**. Akdis C A (Reprint); Blaser K. SWISS INST ALLERGY & ASTHMA RES, OBERE STR 22, CH-7270 DAVOS, SWITZERLAND (Reprint). REVUE FRANCAISE D ALLERGOLOGIE ET D IMMUNOLOGIE CLINIQUE (APR 2000) Vol. 40,

No. 3, pp. 309-317. Publisher: EXPANSION SCI FRANCAISE. 31 BLVD LATOUR MAUBOURG, 75007 PARIS, FRANCE. ISSN: 0335-7457. Pub. country: SWITZERLAND. Language: English.

L5 ANSWER 5 OF 8 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:757120 The Genuine Article (R) Number: 241UT. **Peptide immunotherapy**. Muller U R (Reprint). ZIEGLERSPITAL BERN, MED KLIN, MORILLONSTR 75-91, CH-3001 BERN, SWITZERLAND (Reprint). ALLERGY (OCT 1999) Vol. 54, Supp. [56], pp. 45-46. Publisher: MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0105-4538 . Pub. country: SWITZERLAND. Language: English.

L5 ANSWER 6 OF 8 MEDLINE DUPLICATE 2
1998311035 Document Number: 98311035. PubMed ID: 9648701. Successful immunotherapy with T-cell epitope peptides of bee venom

phospholipase A2 induces specific T-cell anergy in patients allergic to bee venom. Muller U; Akdis C A; Fricker M; Akdis M; Blesken T; Bettens F; Blaser K. (Medical Division, Zieglerspital, Bern, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1998 Jun) 101 (6 Pt 1) 747-54. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Specific immunotherapy with honeybee venom (BV) is highly effective, but allergic side effects can occur during treatment. Immunotherapy with peptides containing major T-cell epitopes of the relevant allergen or allergens provides an alternative strategy without these problems. OBJECTIVE: The study investigates the immunologic mechanisms and clinical effects of immunotherapy with T-cell epitope peptides of the major BV allergen, the **phospholipase A2** (PLA). METHODS: Five patients with IgE-mediated systemic allergic reactions to bee stings were treated with a mixture of three T-cell epitope peptides of PLA. Ten patients allergic to BV receiving whole BV immunotherapy served as control subjects. Increasing doses of the peptide mixture, up to a maintenance dose of 100 microg, were administered subcutaneously within 2 months. The patients were then challenged with

PLA and 1 week later with a bee sting. The cellular and humoral immune response was measured in vitro. RESULTS: No allergic side effects were caused by the **peptide immunotherapy**, and all patients tolerated the challenge with PLA without systemic allergic symptoms. Two patients developed mild systemic allergic reactions after the bee sting challenge. After **peptide immunotherapy**, specific proliferative responses to PLA and the peptides in peripheral blood mononuclear cells were decreased in successfully treated patients. The production of TH2 and TH1 cytokines was inhibited, and B cells were not affected in their capacity to produce specific IgE and IgG4 antibodies. Their levels increased after allergen challenge in favor of IgG4. CONCLUSIONS: Immunotherapy of BV allergy with short T-cell peptides of

PLA induces epitope-specific anergy in peripheral T cells and changes the specific isotype ratio in a fashion similar to that of conventional immunotherapy in successfully treated patients.

L5 ANSWER 7 OF 8 MEDLINE DUPLICATE 3
97400299 Document Number: 97400299. PubMed ID: 9257793. Modulation of T-cell response to **phospholipase A2** and **phospholipase A2**-derived peptides by conventional bee venom immunotherapy. Kammerer R; Chvatchko Y; Kettner A; Dufour N; Corradin G; Spertini F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1997 Jul) 100 (1) 96-103. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Immunologic mechanisms of desensitization are still incompletely understood. Safer methods of immunotherapy with reduced

risks of anaphylaxis need to be developed. OBJECTIVE: To study the effects of conventional venom immunotherapy (VIT) on **phospholipase A2** (PLA2)-specific T cells and on T-cell reactivity to short and long synthetic peptides that map the PLA2 molecule. METHOD: Proliferation of a CD4+ cell-enriched peripheral blood mononuclear cell fraction and cytokine secretion by T cell lines from patients hypersensitive to bee venom and undergoing VIT in response to PLA2 and PLA2 synthetic peptides

were measured. RESULTS: T-cell proliferation in response to three synthetic peptides, 40 to 60 amino acids long and mapping the entire PLA2 molecule with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to

134)

steadily increased during the first 14 weeks of VIT corresponding to the treatment period with incremental doses of antigen. These results are in contrast to the low proliferation indices obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the molecule with short peptides. At the end of VIT (after 3 to 5 years), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by a shift in the pattern of cytokine secretion by T cell lines from a T(H0)-type to a T(H1)-type pattern. CONCLUSION: After a transient increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of cytokine secretion from a T(H0)-type to a T(H1)-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 molecule appear to be efficient T cell stimulators and may represent potential candidates for **peptide immunotherapy**

L5 ANSWER 8 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
97220357 EMBASE Document No.: 1997220357. [Immunotherapy with T cell peptides

of bee venom **phospholipase A2**]. IMMUNOTHERAPIE MIT T-ZELL-PEPTIDEN DER BIENENGIFT-**PHOSPHOLIPASE A2**. Muller U.R.; Akdis C.A.; Fricker M.; Blaser K.. Prof. Dr. U.R. Muller, Zieglerspital, Medizinische Klinik, CH-3007 Bern, Switzerland. Allergo Journal 6/SUPPL. 1 (S53-S54) 1997.

Refs: 6.

ISSN: 0941-8849. CODEN: ALJOEY. Pub. Country: Germany. Language: German. Summary Language: German; English.

AB 5 patients with a history of bee sting allergy and strongly positive skin tests as well as high titers of bee venom and **phospholipase A2**-specific IgE serum antibodies underwent immunotherapy with an equimolar mixture of three T cell peptides of the major bee venom allergen

phospholipase A2. A cumulative dose of around 40 .mu.g of the peptide mixture was applied. All patients tolerated a first provocation test with native **phospholipase A2** without systemic allergic symptoms, while 2 showed mild symptoms following a sting provocation test. In vitro studies suggest induction of allergen-specific T cell anergy by **peptide immunotherapy**.

=> s 11 and hyaluronidase

L6 0 L1 AND HYALURONIDASE

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FILE 'MEDLINE, EMBASE, SCISEARCH, BIOSIS, CAPLUS' ENTERED AT 12:21:22 ON 23 JUL 2001

L1 189 S PEPTIDE IMMUNOTHERAPY

L2 30 S L1 AND BEE VENOM
 L3 14 DUP REMOVE L2 (16 DUPLICATES REMOVED)
 L4 19 S L1 AND PHOSPHOLIPASE A2
 L5 8 DUP REMOVE L4 (11 DUPLICATES REMOVED)
 L6 0 S L1 AND HYALURONIDASE

=> s l1 and hyaluronidase

L7 0 L1 AND HYALURONIDASE

=> s l1 and allergen c

L8 0 L1 AND ALLERGEN C

=> s l1 and mellitin

L9 0 L1 AND MELLITIN

=> s l1 and adolapin

L10 0 L1 AND ADOLAPIN

=> s adolapin

L11 22 ADOLAPIN

=> s l11 and mellitin

L12 0 L11 AND MELLITIN

=> dup remove l11

PROCESSING COMPLETED FOR L11

L13 11 DUP REMOVE L11 (11 DUPLICATES REMOVED)

=> s l13 and bee

L14 11 L13 AND BEE

=> d l14 1-11 cbib abs

L14 ANSWER 1 OF 11 MEDLINE

86022057 Document Number: 86022057. PubMed ID: 2996298. Further investigation on the antiinflammatory properties of **adolapin**--**bee** venom polypeptide. Koburova K L; Michailova S G; Shkenderov S V. ACTA PHYSIOLOGICA ET PHARMACOLOGICA BULGARICA, (1985) 11 (2) 50-5. Journal code: 1SL; 7512568. ISSN: 0323-9950. Pub. country: Bulgaria. Language: English.

AB **Adolapin** is a basic polypeptide (M. W. 11500) isolated from **bee** venom. It showed marked antiinflammatory and analgetic properties and inhibited cyclooxygenase. It was found that **adolapin** inhibited also the activity of **bee** venom phospholipase A2 (7 nmole/ml producing about 80% inhibition of 2.5 nmole/ml phospholipase). In addition it inhibited the lipoxxygenase from human platelets (4.5 nmole/ml inhibited about 80% of the activity of 0.8 mg protein/ml). **Adolapin** (20 micrograms/kg) caused an elevation of c-GMP level in rat spleen and brain as well as a decrease of c-AMP in

rat spleen. **Adolapin** was tested by the "tail flick" method which allowed the demonstration of its analgetic action. The partial inhibition of the analgetic effect of **adolapin** induced by naloxon, proved the participation of a central mechanism of action. Similar to other nonsteroid analgetics, **adolapin** displayed antipyretic effect (40 micrograms/kg caused an inhibition of the mean temperature rise about 62%.

L14 ANSWER 2 OF 11 MEDLINE
85101057 Document Number: 85101057. PubMed ID: 6440766. [Antipyretic effect of a polypeptide from **bee** venom--**adolapin**].
Antipiretichen efekt na edin polipeptid ot pchelnata otrova--
adolapin. Koburova K; Mikhailova S; Shkenderov S. EKSPERIMENTALNA MEDITSINA I MORFOLOGIJA, (1984) 23 (3) 143-8. Journal code: EEB; 0007506.
ISSN: 0367-0643. Pub. country: Bulgaria. Language: Bulgarian.

L14 ANSWER 3 OF 11 MEDLINE
82200186 Document Number: 82200186. PubMed ID: 7080045. **Adolapin** --a newly isolated analgetic and anti-inflammatory polypeptide from **bee** venom. Shkenderov S; Koburova K. TOXICON, (1982) 20 (1) 317-21. Journal code: VWT; 1307333. ISSN: 0041-0101. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Adolapin** was isolated by a two-step procedure: gel filtration and chromatography on CM cellulose. The molecular mass of the polypeptide as determined by SDS electrophoresis and amino acid composition proved to be 11500 and 11092 respectively. **Adolapin** exhibited a potent analgesic effect demonstrated by the "writhing" test (ED50-0,016mg/kg) and by the Randall-Sellito's test (ED50-0,013 mg/kg). The anti-inflammatory activity of **adolapin** was most marked with regard to carrageenin, prostaglandin and adjuvant rat hind paw edemas and adjuvant polyarthritis.

The **adolapin** effects are presumably due to its capacity to inhibit the prostaglandin synthase system, following a biphasic dose-response relationship. It is likely that central mechanisms are also involved in the analgetic action of **adolapin**.

L14 ANSWER 4 OF 11 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
92154432 EMBASE Document No.: 1992154432. [Wasp and **bee** venom allergies]. WESPE- EN BIJEGIFALLERGIEEN. Kochuyt A.M.. Kliniek voor Inwendige Ziekten, Afdeling Klinische Immunologie, Universitaire Ziekenhuizen, Leuven, Belgium. Tijdschrift voor Geneeskunde 48/8 (565-575) 1992.
ISSN: 0371-683X. CODEN: TGEKBW. Pub. Country: Belgium. Language: Dutch. Summary Language: Dutch.

L14 ANSWER 5 OF 11 SCISEARCH COPYRIGHT 2001 ISI (R)
87:45520 The Genuine Article (R) Number: F6986. **BEE** VENOM **ADOLAPIN** - EFFECT ON THROMBOXANE-A2 AND PROSTACYCLINE PLASMA-LEVELS IN RATS WITH MODEL ACUTE-INFLAMMATION. SHKENDEROV S V (Reprint); KOBOUROVA K A; CHAVDAROVA V. STATE INST CONTROL DRUGS, BU-1000 SOFIA, BULGARIA (Reprint). DOKLADI NA BOLGARSKATA AKADEMIYA NA NAUKITE (1986) Vol. 39, No. 9, pp. 155-157. Pub. country: BULGARIA. Language: ENGLISH.

L14 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2001 ACS

- 1985:540101 Document No. 103:140101 **Adolapin** effect on histamine release by rat peritoneal mastocytes. Mikhailova, S.; Koburova, K.; Shkenderov, S. (Bulg.). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 18, 39-43 (Bulgarian) 1985. CODEN: IDISD4. ISSN: 0323-9438.
- AB The effect of **adolapin**, a basic polypeptide of **bees** venom with mol. wt. 11,500, on histamine release by peritoneal mastocytes of rats was investigated. Histamine concn. was detd. by a modification of the spectrofluorometric method. At concn. ranging from 0.1 mcg/mL to 200 mcg/mL **adolapin** caused no histamine release whatsoever. At concns. ranging from 1 mcg/mL to 20 mcg/mL, there was up to 60% inhibition of histamine release, provoked by compd. 48/80 (0.3 mcg/mL). The effect of the calcium ionophore A23187 (0.3 mcg/mL) was not influenced by the polypeptide concns. tested. The possible relationship between **adolapin**-induced inhibition of histamine release and its effect on the metab. of arachidonic acid is discussed.
- L14 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2001 ACS
1984:449848 Document No. 101:49848 Antigenicity of **bee** venom and some of its components. Grigorova, K.; Gencheva, G. (Bulg.). Probl. Infect. Parasit. Dis., 10, 113-16 (English) 1983. CODEN: PIPDD4. ISSN: 0204-9155.
- AB The antigenicity of **bee** venom and fraction 1 from **bee** venom was heterogeneous, with .ltoreq.6 and .ltoreq.5 antigen components, resp., being differentiated. Antisera against phospholipase A2 [9001-84-7] and lysophospholipase [9001-85-8] were prepd. and used to demonstrate an antigenic resemblance between the enzymes present in the **bee** venom. Pptg. antibodies against **adolapin** [79029-92-8] could not be prepd. suggesting that **adolapin** was a considerably weaker antigen than the high-mol.-wt. venom components or was an inactive antigen for the exptl. animals used. IgG fractions were isolated from all antisera obtained.
- L14 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2001 ACS
1984:61381 Document No. 100:61381 Anti-inflammatory activity in the venom of *Apis mellifera* (the common European honey **bee**). Banks, Barbara E. C.; Dempsey, Christopher E.; Barboni, E. (Dep. Physiol., Univ. Coll. London, London, WC1E 6BT, UK). Toxicon, Suppl. 3, 29-32 (English) 1983. CODEN: TOXIA6. ISSN: 0041-0101.
- AB Peptide 401 [32908-73-9] and [des Ile]peptide 401 [88640-95-3] but not the transaminated form of peptide 401 caused release of histamine from rat peritoneal mast cells. Therefore, an N-terminal amino group may be essential for the obsd. biol. activity of this **bee** venom constituent peptide. Rats sensitized with *Nippostrongylus brasiliensis* and then challenged with an allergen reduced the swelling caused by carrageenan. Thus, histamine releasing and inflammation inhibiting activities are closely linked. Fractionation of *A. mellifera* venom was carried out unsuccessfully to identify **adolapin** [79029-92-8] as a high-mol.-wt. peptide with antiinflammatory activity.
- L14 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2001 ACS
1984:1839 Document No. 100:1839 Anaphylactogenic and antigenic properties of

adolapin, a polypeptide isolated from **bee** venom.
Koburova, K.; Grigorova, K.; Shkenderov, S.; Gencheva, G. (Bulg.). Izv.

Durzh. Inst. Kontrol Lek. Sredstva, 16, 95-9 (Bulgarian) 1983. CODEN:
IDISD4. ISSN: 0323-9438.

- AB Double radial immunodiffusion in agar gel demonstrated that during prolonged immunization of rabbits, **adolapin** [79029-92-8] fails to produce pptg. antibodies. **Adolapin** proves to be a weak anaphylactogen since anaphylactic reactions are obsd. in guinea pigs at doses exceeding as much as 125 times the therapeutic one.

L14 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2001 ACS
1981:561805 Document No. 95:161805 Lipoxygenase inhibiting activity of **adolapin** - an antiinflammatory polypeptide from **bee** venom. Koburova, K.; Shkenderov, S. (USSR). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 14, 51-4 (Bulgarian) 1981. CODEN: IDISD4.

- AB **Adolapin** [79029-92-8], a peptide from **bee** venom with antiinflammatory activity, inhibits lipoxygenase [9029-60-1]. The max. effect (42% inhibition) is obtained after 15 min preincubation of 2 .times. 10-6M **adolapin** with the enzyme.

L14 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2001 ACS
1981:97051 Document No. 94:97051 Analgetic effect of **bee** venom and of its **adolapin** peptide components with analgetic and inhibitory effects on prostaglandin synthetase. Shkenderov, S.; Koburova, K. (Bulg.). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 13, 131-3 (Bulgarian)
1980. CODEN: IDISD4.

- AB Analgetic doses (median ED) of crude **bee** venom in the Hendershot mouse test and Randall-Selito rat test were 0.150 and 0.138 mg/kg, resp. Corresponding values for the fraction OA, making up .apprx.25% of lyophilized venom, were 0.022 and 0.020 mg/kg. This fraction had a strong antiinflammatory effect, and at 0.05 mg/kg inhibited by 95% abdominal contractions caused by prostaglandin E. During ion exchange chromatog. of the OA fraction on CM-cellulose, 5 peaks are obtained, the 1st 2 contg. homogeneous peptides named **adolapin** I [76559-67-6] and **adolapin** II [76559-68-7] by the authors. They exert a strong analgetic effect. The latter is explained by the prostaglandin synthetase [9055-65-6] inhibition verified in tests on cat spleen and rat brain.

=> s hyaluronidase

L15 22264 HYALURONIDASE

=> s l15 and bee venom

L16 308 L15 AND BEE VENOM

=> s l16 and therapy

L17 36 L16 AND THERAPY

=> s l17 and vaccine

L18 0 L17 AND VACCINE

=> dup remove l17

PROCESSING COMPLETED FOR L17

L19 27 DUP REMOVE L17 (9 DUPLICATES REMOVED)

=> s l19 and PLA2

L20 1 L19 AND PLA2

=> d l20 cbib abs

L20 ANSWER 1 OF 1 MEDLINE

84008879 Document Number: 84008879. PubMed ID: 6619452. Antibodies to purified **bee venom** proteins and peptides. II. A detailed study of changes in IgE and IgG antibodies to individual **bee venom** antigens. Kemeny D M; MacKenzie-Mills M; Harries M G; Youlten L J; Lessof M H. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1983 Oct) 72 (4) 376-85. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB Antibodies to individual **bee venom** antigens were studied in detail in nine bee sting-allergic patients who received venom immunotherapy without side effects, in two patients who failed to reach maintenance, and in two whose sensitivity returned. The study was

confined

to patients who had IgE antibodies to at least one of four purified **bee venom** antigens at the start of treatment. IgE and IgG antibodies to phospholipase A2 (**PLA2**), **hyaluronidase** (**HYAL**), and acid phosphatase (**ACID P**) and IgE antibodies to melittin

(MEL)

were measured, and changes in the antibody levels were followed during **bee venom** immunotherapy. Two contrasting patterns of antibody response were seen in the nine successfully treated patients. In five patients there was a rise in serum IgG antibodies to the same antigens as the IgE antibodies. In two patients' serum IgE antibody to **HYAL** or **ACID P** fell without a marked IgG antibody response to these antigens, although high levels of IgG antibody to **PLA2** were present in both. Although the first pattern is consistent with a "blocking" role for IgG antibody, clearly the second is not. Not all patients can be conveniently divided into these two categories, and two patients did not show any significant change in either IgG or IgE

antibody

but were nevertheless able to tolerate the maintenance dose of 100 micrograms of venom. Two patients who failed to reach the maintenance

dose

of 100 micrograms because of their allergic reactions to the injections

of

venom were distinguished by (1) very high serum IgE antibody and (2) a

low

ratio of IgG/IgE antibody. Passive immunization with IgG antibody from a hyperimmune beekeeper was, however, protective in these patients,

although

it did not raise their overall serum IgG antibody level very much. We are unable to explain either the failure of conventional **therapy** or the beneficial effect of passive immunization in these two patients. Two bee sting--allergic beekeepers lost their sensitivity to stings, but

later, when their sera contained IgE antibody to another **bee venom** antigen, they reacted to stings and inhalation of beehive dander. These data suggest that either falling IgE antibody or IgG- "blocking" antibody could be responsible for providing clinical protection to **bee venom**--allergic subjects. Renewed clinical sensitivity was observed when the IgE response was modulated, with patients making IgE antibody first to one antigen and then to another.

=> s minimize

L21 6 MINIMINE

=> dup remove l21

PROCESSING COMPLETED FOR L21
L22 3 DUP REMOVE L21 (3 DUPLICATES REMOVED)

=> d l22 1-3 cbib abs

L22 ANSWER 1 OF 3 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 1
97:141382 The Genuine Article (R) Number: WG615. Chromatographic and membrane

purification of polypeptide compounds from honey bee venom.

Klyushnichenk

o V E (Reprint); Syagailo Y V. RUSSIAN ACAD SCI, SHEMYAKIN & OVCHINNIKOV
INST BIOORGAN CHEM, MOSCOW 117871, RUSSIA. JOURNAL OF NATURAL TOXINS (FEB
1997) Vol. 6, No. 1, pp. 111-119. Publisher: ALAKEN, INC. 305 W MAGNOLIA
ST, STE 196, FT COLLINS, CO 80521. ISSN: 1058-8108. Pub. country:

RUSSIA.

Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The compounds of venom *Apis mellifera* contains a set of polypeptides:
melittin, phospholipase A2, apamin, MCD-peptide, **minimine**, and
other substances. The traditional schemes of purification of honey bee
venom earlier included different types of chromatography. The present

work proposes the combination of chromatographic and membrane methods for
purification of honey bee venom. The main advantage of membrane
purification is that melittin in water exists as a monomer (2.7 kD) but

at high salt concentration as a tetramer.

Phospholipase A2 may exist as a monomer (15.4 kD) and a dimer similar
to melittin. The purification scheme covers: alcohol sedimentation,
separation of melittin from the rest of phospholipase A2 by means of
membranes with exclusion limit of 15 and 5 kD, ion exchange and scale up
RP HPLC of melittin. Each step of purification was analyzed by RP HPLC.
The purity of the final product under different chromatographic

conditions

was compared. The melittin was purified from the impurities more than 98%
by RP HPLC.

L22 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
1986:181060 Document No.: BR30:92932. ACUTE RENAL FAILURE DUE TO MULTIPLE
STINGS BY AFRICANIZED BEES. MEJIA G; ARBELAEZ M; HENAO J E; SUS A A;
ARANGO J L. AP AEREO 60417, MEDELLIN, COLOMBIA, SOUTH AMERICA.. Ann.

Intern. Med., (1986) 104 (2), 210-211. CODEN: AIMEAS. ISSN: 0003-4819.
Language: English.

L22 ANSWER 3 OF 3 MEDLINE DUPLICATE 2
72049998 Document Number: 72049998. PubMed ID: 5001226. Polypeptides
minimine and melittin from bee venom: effects on Drosophila. Lowy
P H; Sarmiento L; Mitchell H K. ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS,
(1971 Jul) 145 (1) 338-43. Journal code: 6SK; 0372430. ISSN: 0003-9861.
Pub. country: United States. Language: English.

=> s acid phosphatase

L23 95436 ACID PHOSPHATASE

=> s l23 and bee venom

L24 91 L23 AND BEE VENOM

=> s l24 and desensitization

L25 2 L24 AND DESENSITIZATION

=> dup remove l25

PROCESSING COMPLETED FOR L25

L26 2 DUP REMOVE L25 (0 DUPLICATES REMOVED)

=> d l26 1-2 cbib abs

L26 ANSWER 1 OF 2 MEDLINE
89277565 Document Number: 89277565. PubMed ID: 2499550. Analysis of
differing patterns of cross-reactivity of honeybee and yellow jacket
venom-specific IgE: use of purified venom fractions. Wypych J I;

Abeyounis

C J; Reisman R E. (Department of Medicine, State University of New York,
Buffalo.) INTERNATIONAL ARCHIVES OF ALLERGY AND APPLIED IMMUNOLOGY,
(1989) 89 (1) 60-6. Journal code: GP9; 0404561. ISSN: 0020-5915. Pub.
country: Switzerland. Language: English.

AB Prior studies of sera from insect sting-allergic patients have analyzed
the relationship of coexisting honeybee venom- and yellow jacket
venom-specific IgE. Radioallergosorbent (RAST)-inhibition tests with
these

venoms revealed four different patterns of activity. In this present
study, purified fractions prepared from these venoms were used to analyze
these varying patterns. The hyaluronidases of yellow jacket venom and
honeybee venom showed extensive cross-reaction. The phospholipases from
these venoms showed minimal cross-reactivity; antigen 5 was restricted to
yellow jacket venom. There was a high molecular weight component in

yellow

jacket venom with immunologic properties similar to honeybee venom
acid phosphatase. Sera from individual patients showed
quantitative and qualitative differences in the reactions to the major
components of both venoms. The differences in the RAST-inhibition

patterns

in patients with elevated levels of both honeybee venom- and yellow

jacket

venom-specific IgE are accounted for by these differences as well as by differences in the cross-reactivity between the individual components.

L26 ANSWER 2 OF 2 MEDLINE
88165469 Document Number: 88165469. PubMed ID: 3349595. IgE and IgG antibody response to purified **bee-venom** antigens and peptides in four patients who had adverse reactions to immunotherapy. Kemeny D M; Kagey-Sobotka A; Lichtenstein L M; Lessof M H. (Department of Medicine, United Medical Schools, Guy's Hospital, London, U.K.)

CLINICAL

ALLERGY, (1988 Jan) 18 (1) 79-84. Journal code: DBP; 0311172. ISSN: 0009-9090. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The immunological response to individual **bee-venom** allergens was studied in blood samples collected at frequent intervals from four **bee-venom** allergic patients who had suffered systemic allergic reactions to injections of **bee venom** during immunotherapy. All had high IgE antibody levels, at the upper end of the range found in bee-sting allergic patients, and all had antibodies to the minor allergens at the time of the reactions. These did not, however, provide a simple explanation for the reactions that occurred. We were able to observe two interesting phenomena--in one patient IgE antibodies to the individual venom antigens appeared to be 'switched off' sequentially. In another, IgE antibodies to hyaluronidase rose substantially after 4 years of therapy. We believe that these results provide evidence to support the view that the regulation of IgE antibodies is controlled by mechanisms that are both isotype- and antigen-specific.

=> s protease inhibitor

L27 72750 PROTEASE INHIBITOR

=> s 127 and bee venom

L28 33 L27 AND BEE VENOM

=> s 128 and peptide therapy

L29 0 L28 AND PEPTIDE THERAPY

=> s 128 and desensitization

L30 0 L28 AND DESENSITIZATION

=> s 128 and vaccine

L31 0 L28 AND VACCINE

=> s 128 and immune modulation

L32 0 L28 AND IMMUNE MODULATION

=> dup remove 128

PROCESSING COMPLETED FOR L28

L33 19 DUP REMOVE L28 (14 DUPLICATES REMOVED)

=> s 133 and PLAs

L34 0 L33 AND PLAS

=> d 133 1-19 cbib abs

L33 ANSWER 1 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
2001:203619 Document No.: PREV200100203619. Use of thiol redox proteins for
reducing protein intramolecular disulfide bonds, for improving the
quality
of cereal products, dough and baked goods and for inactivating snake, bee
and scorpion toxins. Buchanan, Bob B. (1); Kobrehel, Karoly; Yee, Boihon
C.; Wong, Joshua H.; Lozano, Rosa; Jiao, Jin-an; Shin, Sungho. (1)
Berkeley, CA USA. ASSIGNEE: The Regents of the University of California,
Cupertino, CA, USA. Patent Info.: US 6113951 September 05, 2000.

Official
Gazette of the United States Patent and Trademark Office Patents, (Sep.

5,
2000) Vol. 1238, No. 1, pp. No Pagination. e-file. ISSN: 0098-1133.
Language: English.

AB Methods of reducing cystine containing animal and plant proteins, and
improving dough and baked goods' characteristics is provided which
includes the steps of mixing dough ingredients with a thiol redox protein
to form a dough and baking the dough to form a baked good. The method of
the present invention preferably uses reduced thioredoxin with wheat
flour

which imparts a stronger dough and higher loaf volumes. Methods for
reducing snake, bee and scorpion toxin proteins with a thiol redox (SH)
agent and thereby inactivating the protein or detoxifying the protein in
an individual are also provided. **Protease inhibitors**,
including the Kunitz and Bowman-Birk trypsin inhibitors of soybean, were
also reduced by the NADP/thioredoxin system (NADPH, thioredoxin, and
NADP-thioredoxin reductase). When reduced by thioredoxin, the Kunitz and
Bowman-Birk soybean trypsin inhibitors lose their ability to inhibit
trypsin. Moreover, the reduced form of the inhibitors showed increased
susceptibility to heat and proteolysis by either subtilisin or a protease
preparation from germinating wheat seeds. The 2S albumin of castor seed
endosperm was reduced by thioredoxin. Thioredoxin was reduced by either
NADPH and NADP-thioredoxin reductase or dithiothreitol. Analyses showed
that thioredoxin actively reduced the intramolecular disulfides of the 2S
large subunit, but was ineffective in reducing the intermolecular
disulfides that connect the large to the small subunit. A novel cystine
containing protein that inhibits pullulanase was isolated; thioredoxin
reduction of this protein destroyed or greatly reduced its inhibitory
activity.

L33 ANSWER 2 OF 19 MEDLINE
2000387536 Document Number: 20269158. PubMed ID: 10811021. Role of
various phospholipases A2 and inhibitors in the pathogenesis and
prevention of pancreatic acinar cell necrosis: studies with isolated rat
pancreatic acini. Mossner J; Wessig C; Ogami Y; Keim V. (Department of
Internal Medicine II, University of Leipzig, Germany..
moej@server3.medizin.uni-leipzig.de) . INTERNATIONAL JOURNAL OF
PANCREATOLOGY, (2000 Feb) 27 (1) 29-38. Journal code: IJP; 8703511.

ISSN:
0169-4197. Pub. country: United States. Language: English.

AB BACKGROUND: Phospholipase A2 (PLA2) may play a central role in the

pathogenesis of pancreatic acinar cell necrosis. Several questions, however, are unsolved: Is acinar cell necrosis caused by PLA2 derived from infiltrating leukocytes or from pancreatic PLA2 itself? Does PLA2 cause cellular lysis by the release of lysolecithin from lecithin or by generation of free radicals? The aims of this study were to determine which form of PLA2 is responsible for cellular damage and how to inhibit its action. METHODS: Isolated rat pancreatic acini were prepared by collagenase digestion. Newly synthesized proteins were labeled by 35S-methionine. Acini were incubated in buffer to which various factors, such as porcine pancreatic PLA2 or **bee venom** PLA2, homogenates of either leukocytes or pancreatic homogenates, all with or without lecithin and with or without potential inhibitors (aprotinin, 4-bromophenacylbromide, BM 16.2115, quinacrine, various analogs of arachidonic acid), or free radicals (hydrogen peroxide, xanthine/xanthine oxidase) with or without allo-purinol or dismutase/catalase were added. Cellular destruction was measured by the release of radiolabeled proteins.

RESULTS: PLA2 alone, free radicals, and granulocytes were not harmful to acini within 30 min of incubation. Free radicals caused significant release of radiolabeled proteins only after 3 h of incubation; this release could be inhibited by scavengers. Incubation of pancreatic acini with PLA2 in combination with lecithin caused rapid release of radiolabeled proteins. Addition of high concentrations of enterokinase activated pancreatic homogenates both alone and with lecithin caused release of cellular proteins, suggesting that pancreatic PLA2 uses lecithin from pancreatic membranes as substrate. Almost all tested potential inhibitors of PLA2 were unable to prevent the destruction caused by either pancreatic or **bee venom** PLA2 and lecithin. However, HK 42, a polyunsaturated fatty acid analog, was able to reduce dose dependently the release of acinar proteins caused by pancreatic PLA2 and lecithin. CONCLUSION: Pancreatic PLA2 and not PLA2 from infiltrating leukocytes may play a role in pancreatic acinar cell necrosis. Cellular lysis is caused upon the action of lysolecithin and probably not via the action of free radicals.

L33 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
2000:368945 Document No.: PREV200000368945. Proteolytic activity of africanized honeybee (*Apis mellifera*: hymenoptera, apidae) venom. De Lima, P. R. M.; Brochetto-Braga, M. R. (1); Chaud-Netto, J.. (1) Departamento de Biologia, Instituto de Biociencias, 13506-900, Rio Claro, Sao Paulo Brazil. Journal of Venomous Animals and Toxins, (2000) Vol. 6, No. 1
CITED
APRIL 18, 2000, pp. 1-14. [http://www.scielo.br/cgi-](http://www.scielo.br/cgi-bin/fbpe/fball?got=all&pid=0104-7930&usr=fbpe&lng=en&nrm=iso&sss=1&aut=71981947)

[bin/fbpe/fball?got=all&pid=0104-7930&usr=fbpe&lng=en&nrm=iso&sss=1&aut=71981947](http://www.scielo.br/cgi-bin/fbpe/fball?got=all&pid=0104-7930&usr=fbpe&lng=en&nrm=iso&sss=1&aut=71981947). online. ISSN: 0104-7930. Language: English. Summary Language: English.

AB Some properties of a Africanized honeybee venom proteases were determined by enzymatic assays in solution, electrophoresis in SDS-PAGE, and gel filtration. **Bee venom** extracts were obtained by reservoir disruption, selective dialysis (cut off 12 kDa) to eliminate small components, such as the **protease inhibitor** present in the venom, and then fractionation of the dialyzed extract by

gel filtration on a Sephadex G-100 column. The optimal conditions for the caseinolytic assays were pH 9.5, 2-hour digestion at 37degree C, and 1% casein concentration. The proteolytic activity was also determined by electrophoresis in SDS-PAGE with co-polymerized gelatin with three major bands of 66.0, 41.6, and 25.1 kDa. A principal serine-protease-like mechanism was revealed in the enriched fraction of proteolytic activity.

L33 ANSWER 4 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)

97:6344 The Genuine Article (R) Number: VX807. Toxins affecting K+ channels. Rowan E G (Reprint); Harvey A L. UNIV STRATHCLYDE, DEPT PHYSIOL & PHARMACOL, STRATHCLYDE INST DRUG RES, ROYAL COLL, 204 GEORGE ST, GLASGOW G1 1XW, LANARK, SCOTLAND (Reprint). BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH (DEC 1996) Vol. 29, No. 12, pp. 1765-1780. Publisher: ASSOC BRAS DIVULG CIENTIFICA. FACULDADE MEDICINA, SALA 21, 14049 RIBEIRAO PRETO, SAO PAULO, BRAZIL. ISSN: 0100-879X. Pub. country: SCOTLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Potassium channels are involved in modulating the excitability of neurones by regulating the membrane potential, or by affecting the amount of neurotransmitter released from nerve terminals. Potassium channels are highly diverse and can be activated by either voltage or increased intracellular calcium concentration. The potassium channel forms a highly selective membrane pore. Four subunits each with six membrane-spanning regions (S1-S6) are required to produce a functional pore. Molecular biologists have cloned more than 50 different potassium channel subtypes. Naturally occurring protein toxins have been used to pharmacologically characterize native and cloned potassium channels.

L33 ANSWER 5 OF 19 MEDLINE

97035391 Document Number: 97035391. PubMed ID: 8875913. Inhibition of spiralin processing by the lipopeptide antibiotic globomycin. Beven L; Le Henaff M; Fontenelle C; Wroblewski H. (Equipe "Membranes et Osmoregulation," CNRS URA No. 256, Universite de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France.) CURRENT MICROBIOLOGY, (1996 Nov) 33 (5) 317-22. Journal code: BMW; 7808448. ISSN: 0343-8651. Pub.

country:

United States. Language: English.

AB The cyclic lipopeptide globomycin, a specific inhibitor of signal-peptidase II (Lsp A), proved toxic for the mollicute Spiroplasma melliferum with a minimal inhibitory concentration (MIC) in the range 6.25-12.5 microM, about one order of magnitude higher (that is, less efficient) than **bee-venom** mellitin. SDS-PAGE analysis of cell proteins followed by immunolabeling ("Western blotting") and by crossed immunoelectrophoresis demonstrated that the cleavage of the prespiralin leader peptide was prevented by globomycin. Cell

fractionation

experiments showed that prespiralin was membrane bound and did not accumulate in the cytoplasm or in the culture medium. Furthermore, the

use

of the potential-sensitive fluorescent dye 3,3'-dipropyl-2,2'-thiadicarbocyanine iodide (diS-C3-[5]) revealed that, in contrast to valinomycin and mellitin, globomycin up to 30 microM has no effect on the electrical transmembrane potential of S. melliferum. This indicates that the toxicity of globomycin for spiroplasma cells is mainly if not exclusively owing to the inhibition of spiralin processing. Added to previously published data, these results suggest that spiralin and probably other lipoproteins of mollicutes are acylated and membrane targeted by a mechanism involving notably the processing of the

prelipoprotein precursor by a type II, globomycin-sensitive signal peptidase.

L33 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2001 ACS

1993:471275 Document No. 119:71275 Use of thio redox proteins for reducing disulfide bonds to improve feed and cereal products and to inactivate snake toxins and insect and scorpion venoms. Buchanan, Bob B.; Kobrehel, Karoly; Yee, Boihon C.; Wong, Joshua H.; Lozano, Rosa; Jiao, Jinan (University of California, USA). PCT Int. Appl. WO 9308274 A1 19930429, 199 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US8595 19921008.

PRIORITY: US 1991-776109 19911012; US 1992-935002 19920825.

AB Thiol redox proteins are used to reduce seed proteins such as cereal proteins, enzyme inhibitor proteins, venom toxin proteins, and the intramol. disulfide bonds of certain other proteins. Thioredoxin and glutaredoxin can be used to reduce gliadins, glutenins, albumins, and globulins to improve the characteristics of dough and baked goods and create new doughs, and to reduce cystine-contg. proteins such as amylase and trypsin inhibitors so as to improve the quality of feed and cereal products. A novel pullulanase inhibitor is isolated. Its activity may be inhibited by the thiol redox proteins. The 2S albumins of oil-bearing seeds (e.g., Ricinus communis) can be reduced with thioredoxin. Reduced thiol redox agents can inactivate snake neurotoxins and certain insect and scorpion venom toxins in vitro and to treat the corresponding toxicities in individuals.

L33 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS

1993:507500 Document No.: PREV199396131507. Role of sodium potassium pump in herpes simplex type 1-induced cell fusion: Melittin causes specific reversion of syncytial mutants with the Syn1 mutation to Syn-plus (wild-type) phenotype. Baghian, Abolghasem; Kousoulas, Konstantin G. (1). (1) Dep. Veterinary Microbiology Parasitology, Sch. Veterinary Med., Louisiana State Univ., Baton Rouge, LA 70803 USA. Virology, (1993) Vol. 196, No. 2, pp. 548-556. ISSN: 0042-6822. Language: English.

AB To evaluate the importance of the Na⁺,K⁺ pump and ionic gradients in virus-induced cell fusion, we investigated the effects of melittin, a 26 amino acid bioactive peptide found in honey **bee venom**, on cell fusion caused by HSV-1 syncytial mutants. Melittin inhibited fusion of Vero cells caused by HSV-1 mutant viruses mP(MP), KOS (syn20) and KOS (FFV3) containing the syncytial mutation syn1 in glycoprotein K. However, it did not affect cell fusion caused by mutants HFEM(tsB5) or

KOS amb1511-7 with mutations in glycoprotein B. Melittin caused specific reversion of syn1 mutant virus plaques to syn⁺ (wild-type) plaque morphology, and inhibited virus adsorption and penetration. It also inhibited the Na⁺,K⁺ pump activity, and the binding of 3H-ouabain to the Na⁺,K⁺ pump of infected Vero cells. The Na⁺,K⁺ pump activity of infected Vero cells in comparison to mock-infected cells was significantly decreased. Ouabain, a specific inhibitor of the Na⁺,K⁺ pump, inhibited fusion of Vero cells caused by all syncytial virus strains.

L33 ANSWER 8 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)

93:1395 The Genuine Article (R) Number: KC026. NEUROPHARMACOLOGY OF

POTASSIUM-ION CHANNELS. HARVEY A L (Reprint). UNIV STRATHCLYDE, DEPT
PHYSIOL & PHARMACOL, GLASGOW G1 1XW, SCOTLAND (Reprint); UNIV
STRATHCLYDE,
STRATHCLYDE INST DRUG RES, GLASGOW G1 1XW, SCOTLAND. MEDICINAL RESEARCH
REVIEWS (JAN 1993) Vol. 13, No. 1, pp. 81-104. ISSN: 0198-6325. Pub.
country: SCOTLAND. Language: ENGLISH.

L33 ANSWER 9 OF 19 MEDLINE DUPLICATE 2
88209451 Document Number: 88209451. PubMed ID: 3130091. Inhibition of
beta-bungarotoxin binding to brain membranes by mast cell degranulating
peptide, toxin I, and ethylene glycol bis (beta-aminoethyl
ether)-N,N,N',N'-tetraacetic acid. Schmidt R R; Betz H; Rehm H. (Zentrum
fur Molekulare Biologie, Universitat Heidelberg, Federal Republic of
Germany.) BIOCHEMISTRY, (1988 Feb 9) 27 (3) 963-7. Journal code: A0G;
0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.
AB The presynaptically active snake venom neurotoxin beta-bungarotoxin
(beta-Butx) is known to affect neurotransmitter release by binding to a
subtype of voltage-activated K⁺ channels. Here we show that mast cell
degranulating (MCD) peptide from **bee venom** inhibits
the binding of 125I-labeled beta-Butx to chick and rat brain membranes
with apparent K_i values of 180 nM and 1100 nM, respectively. The
mechanism
of inhibition by MCD peptide is noncompetitive, as is inhibition of
125I-beta-Butx binding by the **protease inhibitor**
homologue from mamba venom, toxin I. Beta-Butx and its binding
antagonists
thus bind to different sites of the same membrane protein. Removal of
Ca²⁺
by ethylene glycol bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid
inhibits the binding of 125I-beta-Butx by lowering its affinity to brain
membranes.

L33 ANSWER 10 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 3
87:45519 The Genuine Article (R) Number: F6986. ANTIINFLAMMATORY EFFECT OF
BEE VENOM PROTEASE INHIBITOR ON A
MODEL SYSTEM OF ACUTE-INFLAMMATION EDEMA. SHKENDEROV S V (Reprint).
STATE
INST CONTROL DRUGS, 26 BLVD VL ZAIMOV, SOFIA, BULGARIA (Reprint). DOKLADI
NA BOLGARSKATA AKADEMIYA NA NAUKITE (1986) Vol. 39, No. 9, pp. 151-154.
Pub. country: BULGARIA. Language: ENGLISH.

L33 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2001 ACS
1987:65598 Document No. 106:65598 Inhibition of complement activity by
certain **bee venom** components. Gencheva, G.;
Shkenderov, S. (State Inst. Drug Control, Sofia, Bulg.). Dokl. Bolg.
Akad. Nauk, 39(9), 137-9 (English) 1986. CODEN: DBANAD. ISSN:
0366-8681.
AB Protein components of **bee venom** decreased the
hemolytic activity of complement. Apamin, but not melittin or the
protease inhibitor in **bee venom**, was
primarily responsible for the activity.

L33 ANSWER 12 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 4
87:37536 The Genuine Article (R) Number: F5416. **BEE VENOM**
PROTEASE INHIBITOR - IMPROVED PURIFICATION METHOD AND
IDENTIFICATION OF 2 MOLECULAR-FORMS. SHKENDEROV S (Reprint); HABERMANN
E;
SAMEJIMA Y. JUSTUS LIEBIG UNIV, INST PHARMACOL, FRANKFURTER STR 107,

GIESSEN 1, FED REP GER (Reprint); STATE INST CONTROL DRUGS, SOFIA, BULGARIA. DOKLADI NA BOLGARSKATA AKADEMIYA NA NAUKITE (1986) Vol. 39, No. 8, pp. 69-71. Pub. country: GERMANY; BULGARIA. Language: ENGLISH.

L33 ANSWER 13 OF 19 MEDLINE

84261515 Document Number: 84261515. PubMed ID: 6086337. Molecular properties of the apamin-binding component of the Ca^{2+} -dependent K^{+} channel. Radiation-inactivation, affinity labelling and solubilization. Schmid-Antomarchi H; Hugues M; Norman R; Ellory C; Borsotto M; Lazdunski M. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1984 Jul 2) 142 (1) 1-6. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST:

Germany,

Federal Republic of. Language: English.

AB Radiation-inactivation was used to assess the functional size of the apamin-binding component of the Ca^{2+} -dependent K^{+} channel. The amount of specific binding of ^{125}I -apamin to receptors in synaptic membranes of rat cortex decayed exponentially with increasing doses of ionizing radiation and target size analysis was consistent with a relative molecular mass of $250\,000 \pm 20\,000$ for the ^{125}I -apamin receptor. Analysis on sodium dodecyl sulfate gels following covalent cross-linking of ^{125}I -apamin to its receptor in a synaptosomal membrane preparation from rat cortex revealed a single labelled polypeptide chain of $M_r = 33\,000 \pm 2000$ in the presence of **protease inhibitors**. Our results suggest that the Ca^{2+} -dependent K^{+} channel from rat cortex is an oligomeric structure of $M_r = 250\,000 \pm 20\,000$ containing an apamin-binding subunit of $M_r = 33\,000 \pm 2000$. The apamin-binding component of the Ca^{2+} -dependent K^{+} channel from rat synaptosomes was solubilized using detergents such as sodium cholate or 3-[(3-cholamidopropyl)dimethylammonio]-1-propane sulfonate. Phospholipids did not increase the stability of the apamin-binding component during the solubilization. Binding of apamin to its solubilized receptor is reversible and saturable. The dissociation constant of the

apamin-receptor

complex is 40-150 pM, the rates constants of association and dissociation being $3.2 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ and $1.4 \times 10^{-4} \text{ s}^{-1}$ respectively. These binding characteristics are similar to those found for the membrane-bound apamin receptor.

L33 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2001 ACS

1977:529131 Document No. 87:129131 Homology of functionally diverse proteins. Strydom, Daniel J. (Nat'l. Chem. Res. Lab., CSIR, Pretoria, S. Afr.). J. Mol. Evol., 9(4), 349-61 (English) 1977. CODEN: JMEVAU.

AB Disulfide-rich proteins of widely differing functions were aligned, using their half-cystinyl residues. This led to the grouping of RNase, phospholipase A, lysozyme, snake venom toxins, bee and scorpion venom peptides, and the plant proteins, potato carboxypeptidase inhibitor, ragweed pollen allergen, mistletoe toxins, and pineapple sulfhydryl **protease inhibitor**, into 1 superfamily of proteins. Very few deletions/insertions were needed to effect alignment; probabilities were calcd. for random occurrence of the matches that were found.

L33 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2001 ACS

1977:183279 Document No. 86:183279 New pharmacobiochemical data on the anti-inflammatory effect of **bee venom**. Shkenderov, S. (Biochem. Dep., Inst. State Control Drugs, Sofia, Bulg.). Anim., Plant Microb. Toxins, Proc. Int. Symp., 4th, Meeting Date 1974, Volume 2, 319-36. Editor(s): Ohsaka, Akira; Hayashi, Kyojo; Sawai, Yoshio.

Plenum:

Page 50

New York, N. Y. (English) 1976. CODEN: 35FUAR.

- AB Chromatog. fractions (Oa, Op, and the **protease inhibitor** [37205-61-1]) and pure proteins and peptides from **bee venom** (melittin [37231-28-0], apamin [24345-16-2], and phospholipase A [9001-84-7]) were tested in accordance with some of the tests for nonsteroid anti-inflammatory drugs. Adjuvant arthritis, with doses of 100 .mu.g/kg, was weakly affected by melittin and apamin and moderately affected by the **protease inhibitor** and the fractions Oa and Op. Phospholipase A aggravated the development of adjuvant inflammation. The inflammatory rise of the levels of haptoglobin and .beta.-glucuronidase with adjuvant arthritis was considerably inhibited under the effect of the **bee venom** components examd., with the exception of phospholipase, which does not manifest any inhibitory effect. Seromucoid and haptoglobin also decreased in the case of granuloma pouch and turpentine inflammation under the effect of apamin. In the hind paw edema tests, the inhibition of the carrageenin and prostaglandin E1 inflammation under the effects of Oa and Op fractions and the **protease inhibitor** show immunosuppressive actions. The test for protection of denaturation of the serum proteins was pos. with melittin and apamin. The Oa fraction strongly inhibited gelatin-induced aggregation of erythrocytes. Melittin and the **protease inhibitor** inhibited macrophage migration.

L33 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2001 ACS

1977:167002 Document No. 86:167002 Further purification, inhibitory spectrum, and some kinetic properties of the **protease inhibitor** in **bee venom**. Shkenderov, S. (Inst. State Control Drugs, Sofia, Bulg.). Anim., Plant Microb. Toxins, Proc. Int. Symp., 4th, Meeting Date 1974, Volume 1, 263-72. Editor(s): Ohsaka, Akira; Hayashi, Kyojo; Sawai, Yoshio. Plenum: New York, N. Y. (English) 1976. CODEN: 35FUAR.

- AB A polyvalent proteinase inhibitor was purified from **bee venom** by gel filtration on Sephadex G-50, chromatog. on SP-Sephadex C-25, affinity chromatog. on trypsin-Sepharose, and gel filtration on Sephadex G-15, which resulted not only in desalting but in further sepn. The purified inhibitor was homogeneous as judged by polyacrylamide gel electrophoresis and N-terminal amino acid anal. The N-terminal amino acid was L-lysine. The inhibitory spectrum of the **bee venom** inhibitor strongly resembled Trasylol except that it did not inhibit kallikrein or urokinase. Trypsin and chymotrypsin

were most strongly inhibited. Inhibition of trypsin hydrolysis of casein was noncompetitive, whereas inhibition of trypsin amidase activity toward N-benzoyl-DL-arginine-p-nitroanilide was competitive. Inhibition of esterase activities of trypsin and chymotrypsin (toward N-benzoyl-DL-arginine Et ester and N-acetyl-L-tyrosine Et ester, resp.) was competitive. The highest inhibitory activity was obsd. at the onset of the reaction and the inhibitor was thus classified as fast-acting.

L33 ANSWER 17 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5 76024135 EMBASE Document No.: 1976024135. Further purification, inhibitory spectrum and kinetic properties of **protease inhibitor** in **bee venom**. Shkenderov S.. Inst. State Contr. Drugs, Sofia, Bulgaria. Toxicon 13/2 (124) 1975. CODEN: TOXIA6. Language: English.

L33 ANSWER 18 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
75098812 EMBASE Document No.: 1975098812. Anaphylactogenic properties of
bee venom and its fractions. Shkenderov S.. Inst. State
Contr. Drugs, Sofia, Bulgaria. Toxicon 12/5 (529-534) 1974.
CODEN: TOXIA6. Language: English.

AB The author investigated the anaphylactogenicity of whole **bee venom** and its pure protein and peptide components (phospholipase A, melittin and apamin) and the partially purified protein and peptide fractions (the highest mol wt fraction I, hyaluronidase, fractions Op, P1 and P2 and **protease inhibitor**) obtained by means of gel filtration and ion exchange chromatography. Anaphylactogenicity was observed with the whole **bee venom** and the high mol wt protein fractions: fraction I, phospholipase A and hyaluronidase. The peptides melittin, apamin, fraction Op (mast cell degranulating peptide, MCD) and fractions P1 and P2 did not show any anaphylactic properties after sensitization with or without Freund's complete adjuvant.

L33 ANSWER 19 OF 19 MEDLINE DUPLICATE 7
73248122 Document Number: 73248122. PubMed ID: 4728973. A
protease inhibitor in bee venom.
Identification, partial purification and some properties. Shkenderov S.
FEBS LETTERS, (1973 Jul 15) 33 (3) 343-7. Journal code: EUH; 0155157.
ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

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L36 172 DUP REMOVE L35 (242 DUPLICATES REMOVED)

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L37 19 L36 AND BEE

=> dup remove 137

PROCESSING COMPLETED FOR L37
L38 19 DUP REMOVE L37 (0 DUPLICATES REMOVED)

=> d 138 1-19 cbib abs

L38 ANSWER 1 OF 19 MEDLINE
2001226583 Document Number: 21142832. PubMed ID: 11207323.
Antigen-independent suppression of the allergic immune response to
bee venom phospholipase A(2) by DNA vaccination in CBA/J mice.

Jilek S; Barbey C; **Spertini F**; Cortes B. (Division of Immunology and Allergy, R & D Laboratory, Centre Hospitalier Universitaire

Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2001 Mar 1) 166 (5) 3612-21. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Phospholipase A(2) (PLA(2)) is one of the major honey **bee** venom allergens for humans. To assess the long-term prevention of allergic reactions by DNA vaccination, a PLA(2)-CBA/J mouse model was employed using empty or PLA(2) sequence-carrying DNA plasmids. Early skin application of either DNA construct before (prophylactic approach) or after (therapeutic approach) sensitization with PLA(2)/alum led to reduced

PLA(2)-specific IgE and IgG1 titers at 7 mo, with concomitant rise in IgG2a and IgG3. Splenocytes recovered at 5-6 mo after the last DNA administration exhibited a sustained IFN-gamma and IL-10 secretion and reduced IL-4 production. Recall challenge with PLA(2) boosted IFN-gamma and IL-10 secretion, suggesting the reactivation of quiescent memory Th1 lymphocytes. Mice from the prophylactic groups were fully protected against anaphylaxis, whereas 65% of the animals recovered in the therapeutic groups. Th1-polarized immune responses were also active in mice vaccinated with an empty plasmid 32 wk before sensitization with another Ag (OVA). This is the first demonstration that the Ag-coding sequence in DNA vaccine is not necessary to promote immune modulation in naive and sensitized animals for a prolonged period, and has relevance

for the understanding of the innate and induced mechanisms underlying gene immunotherapy in long-term treatment of allergy.

L38 ANSWER 2 OF 19 MEDLINE
2001242064 Document Number: 21242713. PubMed ID: 11344362. Api m 6: a new

bee venom allergen. Kettner A; Hughes G J; Frutiger S; Astori M; Roggero M; **Spertini F**; Corradin G. (Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (2001 May) 107 (5) 914-20. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Characterization of the primary structure of allergens is a prerequisite for the design of new diagnostic and therapeutic tools for allergic diseases. OBJECTIVE: The purpose of this study was the identification and characterization of a low-molecular-weight, IgE-binding, **bee** venom (BV) allergen. METHODS: BV proteins were separated by using size exclusion chromatography and HPLC. IgE antibody binding to purified proteins was analyzed by means of immunoblotting, and T-cell response was analyzed by means of proliferation assay. Amino acid sequence was determined with 2 approaches, namely Edman degradation and carboxy terminal analysis with mass spectrometry. RESULTS: Api m 6, which migrated as an 8-kd band in SDS-PAGE, was frequently (42%) recognized by IgE from BV-hypersensitive patients. In addition, PBMCs from BV-hypersensitive patients, as well as from a normal control subject, proliferated in response to this allergen. Api m 6 exists as 4 isoforms

of 7190, 7400, 7598, and 7808 d, respectively. Amino acid sequences obtained from HPLC-purified preparations revealed that the isoforms were constituted of a common central core of 67 residues, only differing in

the amino- and carboxy-terminal ends. Api m 6 showed no significant sequence homology with known proteins. CONCLUSIONS: We have identified and

sequenced a new BV allergen that elicits a strong IgE and T-cell response in a large number of BV-hypersensitive patients. Api m 6 should be considered in the diagnostic and therapeutic approach of BV immunotherapy on the basis of peptides or recombinant proteins.

L38 ANSWER 3 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:201112 The Genuine Article (R) Number: 405RE. Antigen-independent suppression of the allergic immune response to **bee** venom phospholipase A2 by DNA vaccination in CBA/J mice. Corthesy B (Reprint); Jilek S; Barbey C; **Spertini F.** Hop Orthoped, Lausanne, Switzerland. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (FEB 2001) Vol. 107, No. 2, Supp. [S], pp. S325-S325. MA 1059. Publisher: MOSBY, INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA. ISSN: 0091-6749
. Pub. country: Switzerland. Language: English.

L38 ANSWER 4 OF 19 MEDLINE
2000483268 Document Number: 20432339. PubMed ID: 10975871. Inducing tolerance by intranasal administration of long peptides in naive and primed CBA/J mice. Astori M; von Garnier C; Kettner A; Dufour N; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2000 Sep 15) 165 (6) 3497-505. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To assess the capacity of a peptide-based immunotherapy to induce systemic tolerance via the nasal route, we designed three long overlapping peptides of 44-60 aa covering the entire sequence of phospholipase A2 (PLA2), a major **bee** venom allergen. Both prophylactic and therapeutic intranasal administrations of long peptides to PLA2-hypersensitive CBA/J mice induced specific T cell tolerance to the native allergen. In prophylactic conditions, this tolerance was marked by a suppression of subsequent specific IgE response, whereas the therapeutic approach in presensitized mice induced a more than 60% decrease in PLA2-specific IgE. This decline was associated with a shift in the cytokine response toward a Th1 profile, as demonstrated by decreased PLA2-specific IgG1 and enhanced IgG2a levels, and by a decline in the specific IL-4/IFN-gamma ratios. T cell transfer from long peptide-tolerized mice to naive animals abrogated the expected anti-PLA2 IgE and IgG1 Ab response, as well as specific T cell proliferation, but enhanced specific IgG2a response upon sensitization with PLA2. These events were strongly suggestive of a clonal anergy affecting more profoundly Th2 than the Th1 subsets. In conclusion, these results demonstrate that allergen-derived long peptides delivered via the nasal mucosa may offer an alternative to immunotherapy with native allergens without the inherent risk of systemic anaphylactic reactions. Moreover, long peptides, in contrast to immunotherapy strategies based on short peptides, have the advantage of covering all potential T cell epitopes, and may represent novel and safe tools for the therapy of allergic diseases.

L38 ANSWER 5 OF 19 MEDLINE
2000386468 Document Number: 20354865. PubMed ID: 10898500.
Allergen-derived long peptide immunotherapy down-regulates specific IgE response and protects from anaphylaxis. von Garnier C; Astori M; Kettner

- A; Dufour N; Heusser C; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jun) 30
- (6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
- AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J mice were sensitized with low dose alum-adsorbed phospholipase A2 (PLA2), a major **bee** venom allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides
- (44- to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long peptide mixture were fully protected from anaphylaxis. This indicated that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.
- L38 ANSWER 6 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:192482 The Genuine Article (R) Number: 287WR. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2 derived long peptides in **bee** venom hypersensitive patients. **Spertini F (Reprint)**; Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin G.
- CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO
- 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.
- L38 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2-derived long peptides in **bee** venom hypersensitive patients. **Spertini, Francois (1)**; Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1)
- Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy and Clinical Immunology., (Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary Language: English.

L38 ANSWER 8 OF 19 MEDLINE

1999221995 Document Number: 99221995. PubMed ID: 10202349. IgE and T-cell

responses to high-molecular weight allergens from **bee** venom.

Kettner A; Henry H; Hughes G J; Corradin G; **Spertini F.**

(Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY,

(1999

Mar) 29 (3) 394-401. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: **Bee** venom contains multiple allergens with a wide distribution of molecular weight. In contrast with conventional **bee** venom desensitization, peptide or recombinant allergen immunotherapy may have to take into account patients' individual patterns of humoral or cellular response. OBJECTIVE: To study immunoglobulin (Ig)E and T-cell responses to high-molecular weight **bee** venom allergens ≥ 50 kDa. METHODS: **Bee** venom proteins were separated by size exclusion chromatography and fractions were characterized by one and two-dimensional gel electrophoresis. IgE antibody binding to **bee** venom fractions was analysed by immunoblotting and T-cell responses by proliferation assay. RESULTS: Among 38 **bee** venom-hypersensitive patients, IgE recognition pattern of **bee** venom allergens varied greatly. IgE bound mainly to phospholipase A2 and furthermore to several proteins ≥ 50 kDa (50, 54, 69, 84 and 94 kDa). N-terminal sequences of these proteins showed no homology with known proteins. In addition, peripheral mononuclear cells from patients as well as from nonatopic donors strongly proliferated in response to those proteins. CONCLUSIONS: Although present in low amounts, high-molecular weight allergens from **bee** venom elicit strong IgE and T-cell responses, and may need to be considered as clinically relevant. Therefore, the development of peptide or recombinant protein-based immunotherapy for **bee** venom allergy may require careful characterization of such allergens.

L38 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)

1999:142906 The Genuine Article (R) Number: 165FC. Intranasal administration of long overlapping peptides from **bee** venom phospholipase A2 induces tolerance in hypersensitive CBA/J. Astori M (Reprint);

vonGarnier

C; Corradin G P; **Spertini F.** CHU VAUDOIS, DEPT IMMUNOL & ALLERGY, LAUSANNE, SWITZERLAND; UNIV LAUSANNE, INST BIOCHEM, CH-1015 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1999) Vol. 103, No. 1, Part 2, Supp. [S], pp. 192-192. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO

63146-3318

. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L38 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS

1999:136272 Document No.: PREV199900136272. Intranasal administration of long overlapping peptides from **bee** venom phospholipase A2 induces tolerance in hypersensitive CBA/J mice. Astori, M. (1); Von Garnier, C. (1); Corradin, G. P.; **Spertini, F. (1).** (1) Dep. Immunol.

Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1999) Vol. 103, No. 1 PART 2, pp. S51. Meeting Info.: 55th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3, 1999 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language:

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L1 7518 BEE VENOM

=> s l1 and polypeptide.

L2 502 L1 AND POLYPEPTIDE

=> s l2 and 8 Kd

L3 0 L2 AND 8 KD

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L4 55 L2 AND 8

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L5 3 L4 AND KD

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L6 2 DUP REMOVE L5 (1 DUPLICATE REMOVED)

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L6 ANSWER 1 OF 2 MEDLINE
88082757 Document Number: 88082757. PubMed ID: 2446869. Photoaffinity labeling of the K+-channel-associated apamin-binding molecule in smooth muscle, liver and heart membranes. Marqueze B; Seagar M J; Couraud F. (Laboratoire de Biochimie, Centre National de la Recherche Scientifique Unite Associee 1179, Marseille-France.) EUROPEAN JOURNAL OF BIOCHEMISTRY, (1987 Dec 1) 169 (2) 295-8. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.
AB High-affinity binding sites for mono[125I]iodoapamin were detected in membranes (**Kd** = 59 pM, Bmax = 24 fmol/mg protein) and cultured cells (**Kd** = 69 pM, Bmax = 2.8 fmol/mg protein) from rat heart and in membranes from guinea-pig ileum (**Kd** = 67 pM, Bmax 42 fmol/mg protein) and liver (**Kd** = 15 pM, Bmax = 43 fmol/mg protein). Binding was stimulated by K+ ions (K0.5 = 0.3-0.5 mM). Covalent labeling with arylazide [125I]iodoapamin derivatives showed that smooth muscle, liver and heart binding molecules, are associated with a 85-87-kDa **polypeptide**. A second strongly labeled 57-kDa component was identified in liver membranes only.

L6 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
87133589 Document Number: 87133589. PubMed ID: 3028799.
Receptor-mediated

endocytosis of apamin by liver cells. Strong P N; Evans W H. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1987 Mar 2) 163 (2) 267-73. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB The binding and uptake of the **bee venom** toxin apamin, by guinea-pig and rat liver were studied. Guinea-pig liver plasma membranes contain inhibitable, high-affinity binding sites for [125I]monoiodoapamin: $K_d = 12.6 \pm 0.8$ pM (SE); $B_{max} = 4.2 \pm 0.2$ fmol/mg protein. No binding sites for [125I]monoiodoapamin on rat liver plasma membranes were detected in agreement with the absence of a physiological response to the toxin by rat hepatocytes. [125I]Monoiodoapamin, injected into the portal vein of guinea-pigs, was recovered in an undegraded form in a liver endosome fraction. The uptake of [125I]monoiodoapamin by rat livers was less than 4% of that taken up

by guinea-pig livers and there was little evidence of radiolabelled toxin appearing in isolated rat endocytic vesicles. Inhibitable, high-affinity binding sites for [125I]monoiodoapamin were also identified on isolated guinea-pig liver endosomal membranes; $K_d = 10.6 \pm 3.3$ pM; $B_{max} = 2.5 \pm 0.6$ fmol/mg protein. No inhibitable apamin binding sites were detected on rat endosomal membranes. Plasma membranes and endosomal membranes isolated from guinea-pig liver showed a similar spectrum of **polypeptides** to that previously reported for plasma membranes and endosomal membranes isolated from rat liver. The enzymatic composition of guinea-pig endosomes was also similar to that previously reported for rat endosomes. The results indicate that apamin was internalised by receptor-mediated endocytosis by guinea-pig liver cells in an analogous manner to that already shown for a variety of endogenous ligands.

=> s spertini f?/au

L7 414 SPERTINI F?/AU

=> s 17 and bee venom

L8 45 L7 AND BEE VENOM

=> dup remove 18

PROCESSING COMPLETED FOR L8

L9 19 DUP REMOVE L8 (26 DUPLICATES REMOVED)

=> d 19 1-19 cbib abs

L9 ANSWER 1 OF 19 MEDLINE DUPLICATE 1
2001226583 Document Number: 21142832. PubMed ID: 11207323.
Antigen-independent suppression of the allergic immune response to **bee venom** phospholipase A(2) by DNA vaccination in CBA/J mice. Jilek S; Barbey C; **Spertini F**; Corthesy B. (Division of Immunology and Allergy, R & D Laboratory, Centre Hospitalier Universitaire

Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2001 Mar 1) 166 (5) 3612-21. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Phospholipase A(2) (PLA(2)) is one of the major honey **bee venom** allergens for humans. To assess the long-term prevention of allergic reactions by DNA vaccination, a PLA(2)-CBA/J mouse model was employed using empty or PLA(2) sequence-carrying DNA plasmids. Early skin application of either DNA construct before (prophylactic approach) or after (therapeutic approach) sensitization with PLA(2)/alum led to reduced

PLA(2)-specific IgE and IgG1 titers at 7 mo, with concomitant rise in IgG2a and IgG3. Splenocytes recovered at 5-6 mo after the last DNA administration exhibited a sustained IFN-gamma and IL-10 secretion and reduced IL-4 production. Recall challenge with PLA(2) boosted IFN-gamma and IL-10 secretion, suggesting the reactivation of quiescent memory Th1 lymphocytes. Mice from the prophylactic groups were fully protected against anaphylaxis, whereas 65% of the animals recovered in the therapeutic groups. Th1-polarized immune responses were also active in mice vaccinated with an empty plasmid 32 wk before sensitization with another Ag (OVA). This is the first demonstration that the Ag-coding sequence in DNA vaccine is not necessary to promote immune modulation in naive and sensitized animals for a prolonged period, and has relevance for the understanding of the innate and induced mechanisms underlying gene immunotherapy in long-term treatment of allergy.

L9 ANSWER 2 OF 19 MEDLINE DUPLICATE 2
2001242064 Document Number: 21242713. PubMed ID: 11344362. Api m 6: a new

bee venom allergen. Kettner A; Hughes G J; Frutiger S; Astori M; Roggero M; **Spertini F**; Corradin G. (Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (2001 May) 107 (5) 914-20. Journal code:

H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Characterization of the primary structure of allergens is a prerequisite for the design of new diagnostic and therapeutic tools for allergic diseases. OBJECTIVE: The purpose of this study was the identification and characterization of a low-molecular-weight, IgE-binding, **bee venom** (BV) allergen. METHODS: BV proteins were separated by using size exclusion chromatography and HPLC. IgE antibody binding to purified proteins was analyzed by means of immunoblotting, and T-cell response was analyzed by means of

proliferation assay. Amino acid sequence was determined with 2 approaches, namely Edman degradation and carboxy terminal analysis with mass spectrometry.

RESULTS:

Api m 6, which migrated as an 8-kd band in SDS-PAGE, was frequently (42%) recognized by IgE from BV-hypersensitive patients. In addition, PBMCs from BV-hypersensitive patients, as well as from a normal control subject, proliferated in response to this allergen. Api m 6 exists as 4 isoforms of 7190, 7400, 7598, and 7808 d, respectively. Amino acid sequences obtained from HPLC-purified preparations revealed that the isoforms were constituted of a common central core of 67 residues, only differing in the amino- and carboxy-terminal ends. Api m 6 showed no significant sequence homology with known proteins. CONCLUSIONS: We have identified and sequenced a new BV allergen that elicits a strong IgE and T-cell response in a large number of BV-hypersensitive patients. Api m 6 should be considered in the diagnostic and therapeutic approach of BV immunotherapy on the basis of peptides or recombinant proteins.

L9 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
2001:199768 Document No.: PREV200100199768. Antigen-independent suppression of

the allergic immune response to **bee venom** phospholipase A2 by DNA vaccination in CBA/J mice. Cortesey, Blaise (1); Jilek, Samantha (1); Barbey, Catherine (1); **Spertini, Francois (1)**. (1) Hopital Orthopedique, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (February, 2001) Vol. 107, No. 2, pp. S325. print.

- L9 ANSWER 4 OF 19 MEDLINE DUPLICATE 4
2000483268 Document Number: 20432339. PubMed ID: 10975871. Inducing tolerance by intranasal administration of long peptides in naive and primed CBA/J mice. Astori M; von Garnier C; Kettner A; Dufour N; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2000 Sep 15) 165 (6) 3497-505. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
- AB To assess the capacity of a peptide-based immunotherapy to induce systemic tolerance via the nasal route, we designed three long overlapping peptides of 44-60 aa covering the entire sequence of phospholipase A2 (PLA2), a major **bee venom** allergen. Both prophylactic and therapeutic intranasal administrations of long peptides to PLA2-hypersensitive CBA/J mice induced specific T cell tolerance to the native allergen. In prophylactic conditions, this tolerance was marked by a suppression of subsequent specific IgE response, whereas the therapeutic approach in presensitized mice induced a more than 60% decrease in PLA2-specific IgE. This decline was associated with a shift in the cytokine response toward a Th1 profile, as demonstrated by decreased PLA2-specific IgG1 and enhanced IgG2a levels, and by a decline in the specific IL-4/IFN-gamma ratios. T cell transfer from long peptide-tolerized mice to naive animals abrogated the expected anti-PLA2 IgE and IgG1 Ab response, as well as specific T cell proliferation, but enhanced specific IgG2a response upon sensitization with PLA2. These events were strongly suggestive of a clonal anergy affecting more profoundly Th2 than the Th1 subsets. In conclusion, these results demonstrate that allergen-derived long peptides delivered via the nasal mucosa may offer an alternative to immunotherapy with native allergens without the inherent risk of systemic anaphylactic reactions. Moreover, long peptides, in contrast to immunotherapy strategies based on short peptides, have the advantage of covering all potential T cell epitopes, and may represent novel and safe tools for the therapy of allergic diseases.

- L9 ANSWER 5 OF 19 MEDLINE DUPLICATE 5
2000386468 Document Number: 20354865. PubMed ID: 10898500. Allergen-derived long peptide immunotherapy down-regulates specific IgE response and protects from anaphylaxis. von Garnier C; Astori M; Kettner A; Dufour N; Heusser C; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jun) 30 (6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
- AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J mice were sensitized with low dose alum-adsorbed phospholipase A2 (PLA2), a major **bee venom** allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides (44- to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long

peptide mixture were fully protected from anaphylaxis. This indicated that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L9 ANSWER 6 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:192482 The Genuine Article (R) Number: 287WR. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2 derived long peptides in **bee venom** hypersensitive patients. **Spertini F (Reprint)**; Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin

G. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS,

MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2-derived

long peptides in **bee venom** hypersensitive patients.

Spertini, Francois (1); Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1)

Division

of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy and Clinical

Immunology.,

(Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary Language: English.

L9 ANSWER 8 OF 19 MEDLINE DUPLICATE 6
1999221995 Document Number: 99221995. PubMed ID: 10202349. IgE and T-cell

responses to high-molecular weight allergens from **bee venom**. Kettner A; Henry H; Hughes G J; Corradin G; **Spertini F**. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1999 Mar) 29 (3) 394-401. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: **Bee venom** contains multiple allergens with a wide distribution of molecular weight. In contrast with conventional **bee venom** desensitization, peptide or recombinant allergen immunotherapy may have to take into account patients' individual patterns of humoral or cellular response. OBJECTIVE: To study immunoglobulin (Ig)E and T-cell responses to high-molecular weight **bee venom** allergens ≥ 50 kDa. METHODS: **Bee venom** proteins were separated by size exclusion chromatography and fractions were characterized by one and two-dimensional gel electrophoresis. IgE antibody binding to **bee venom** fractions was analysed by immunoblotting and T-cell responses by proliferation assay. RESULTS: Among 38 **bee venom** -hypersensitive patients, IgE recognition pattern of **bee**

venom allergens varied greatly. IgE bound mainly to phospholipase A2 and furthermore to several proteins ≥ 50 kDa (50, 54, 69, 84 and 94 kDa). N-terminal sequences of these proteins showed no homology with known proteins. In addition, peripheral mononuclear cells from patients as well as from nonatopic donors strongly proliferated in response to those proteins. CONCLUSIONS: Although present in low amounts, high-molecular weight allergens from **bee venom** elicit strong IgE and T-cell responses, and may need to be considered as clinically relevant. Therefore, the development of peptide or recombinant protein-based immunotherapy for **bee venom** allergy may require careful characterization of such allergens.

L9 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:142906 The Genuine Article (R) Number: 165FC. Intranasal administration of long overlapping peptides from **bee venom** phospholipase A2 induces tolerance in hypersensitive CBA/J. Astori M (Reprint); vonGarnier C; Corradin G P; **Spertini F.** CHU VAUDOIS, DEPT IMMUNOL & ALLERGY, LAUSANNE, SWITZERLAND; UNIV LAUSANNE, INST BIOCHEM, CH-1015 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1999) Vol. 103, No. 1, Part 2, Supp. [S], pp. 192-192. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1999:136272 Document No.: PREV199900136272. Intranasal administration of long overlapping peptides from **bee venom** phospholipase A2 induces tolerance in hypersensitive CBA/J mice. Astori, M. (1); Von Garnier, C. (1); Corradin, G. P.; **Spertini, F. (1).** (1) Dep. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1999) Vol. 103, No. 1 PART 2, pp. S51.

Meeting
Info.: 55th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3, 1999 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language: English.

L9 ANSWER 11 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1998:176527 The Genuine Article (R) Number: YW339. Isolation and characterization of a novel 7.6 Kd allergen from **bee venom**. Astori M (Reprint); Kettner A; Frutiger S; Hughes G J; Corradin G; **Spertini F.** CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1998) Vol. 101, No. 1, Part 2, pp. 697-697. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 12 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1998:154406 Document No.: PREV199800154406. Isolation and characterization of a novel 7.6 Kd allergen from **bee venom**. Astori, M.; Kettner, A.; Frutiger, S.; Hughes, G. J.; Corradin, G.; **Spertini, F.** Div. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1998) Vol. 101, No. 1 PART 2, pp. S169. Meeting Info.: 54th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Washington, DC, USA March 13-18, 1998 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language: English.

L9 ANSWER 13 OF 19 MEDLINE DUPLICATE 7
1998341973 Document Number: 98341973. PubMed ID: 9678833. Delineation of

PLA2 epitopes using short or long overlapping synthetic peptides:
interest

for specific immunotherapy. Kammerer R; Kettner A; Chvatchko Y; Dufour N; Tiercy J M; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1997 Sep) 27 (9) 1016-26. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Venom immunotherapy is definitely indicated in severe systemic

anaphylactic reactions to bee stings, but is not devoided of risks of anaphylaxis. Safer methods of immunotherapy need to be developed.

OBJECTIVE: To delineate phospholipase A2 T-cell epitopes using short

15mer

vs long 40-60mer overlapping peptides, and to approach the potential interest of a venom immunotherapy based on the use of long peptides

(1-60,

51-99, 90-134) mapping the whole phospholipase A2 molecule vs a

restricted

number of immunodominant epitopes. METHODS: Proliferation of a CD8+ T

cell

depleted peripheral blood mononuclear cell fraction and short-term T-cell lines from unselected **bee venom** hypersensitive

patients in response to phospholipase A2 synthetic peptides. RESULTS:

Whereas T-cell proliferation to 15mer overlapping peptides was weak,

T-cell response to long overlapping peptides was in contrast vigorous in

all patients, mostly directed to C-terminal peptide 90-134. Our results

did not support the concept of rare dominant T-cell epitopes, and

disclosed T-cell responses to multiple epitopes in several patients. No

significant IgE-binding to long overlapping peptides was detected except

in one patient against peptide 90-134. CONCLUSION: 15mer peptides might

not be sensitive enough to fully delineate all potential T-cell epitopes

scattered along the allergen. Since they do not bind IgE in vitro or only

weakly, and taking into account a T-cell response frequently directed to

multiple epitopes, long overlapping peptides may represent ideal tools

for

immunotherapy.

L9 ANSWER 14 OF 19

MEDLINE

DUPLICATE 8

97400299 Document Number: 97400299. PubMed ID: 9257793. Modulation of

T-cell response to phospholipase A2 and phospholipase A2-derived peptides

by conventional **bee venom** immunotherapy. Kammerer R;

Chvatchko Y; Kettner A; Dufour N; Corradin G; **Spertini F.**

(Division of Immunology and Allergy, Centre Hospitalier Universitaire

Vaudois, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL

IMMUNOLOGY, (1997 Jul) 100 (1) 96-103. Journal code: H53; 1275002. ISSN:

0091-6749. Pub. country: United States. Language: English.

AB

BACKGROUND: Immunologic mechanisms of desensitization are still

incompletely understood. Safer methods of immunotherapy with reduced

risks

of anaphylaxis need to be developed. OBJECTIVE: To study the effects of

conventional venom immunotherapy (VIT) on phospholipase A2 (PLA2)-specific

T cells and on T-cell reactivity to short and long synthetic peptides

that

map the PLA2 molecule. METHOD: Proliferation of a CD4+ cell-enriched

peripheral blood mononuclear cell fraction and cytokine secretion by T

cell lines from patients hypersensitive to **bee venom**

and undergoing VIT in response to PLA2 and PLA2 synthetic peptides were

measured. RESULTS: T-cell proliferation in response to three synthetic

peptides, 40 to 60 amino acids long and mapping the entire PLA2 molecule

with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to 134)

steadily

increased during the first 14 weeks of VIT corresponding to the treatment

period with incremental doses of antigen. These results are in contrast to the low proliferation indices obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the molecule with short peptides. At the end of VIT (after 3 to 5 years), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by a shift in the pattern of cytokine secretion by T cell lines from a T(H0)-type to a T(H1)-type pattern. CONCLUSION: After a transient increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of cytokine secretion from a T(H0)-type to a T(H1)-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 molecule appear to be efficient T cell stimulators and may represent potential candidates for peptide immunotherapy.

L9 ANSWER 15 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
96:400023 The Genuine Article (R) Number: UK861. A NOVEL 7.6 KD ALLERGEN FROM

BEE VENOM - ISOLATION AND CHARACTERIZATION. ASTORI M (Reprint); KETTNER A; FRUTIGER S; HUGHES G J; CORRADIN G; **SPERTINI F.** CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, CH-1066 EPALINGES, SWITZERLAND; CTR MED UNIV GENEVA, DEPT MED BIOL, CH-1211 GENEVA, SWITZERLAND. FASEB JOURNAL (30 APR 1996) Vol. 10, No. 6, pp. 2764. ISSN: 0892-6638. Pub. country: SWITZERLAND.

Language:
ENGLISH.

L9 ANSWER 16 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310225 Document No.: PREV199699032581. T cell epitope mapping with short or long synthetic peptides. Kettner, A. (1); Chvatachko, Y.; Kammerer, R.;

Dufour, N.; Corradin, G. (1); **Spertini, F.** (1) Inst. Biochem., 1066 Epalinges Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp. A1479. Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for

Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

L9 ANSWER 17 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310226 Document No.: PREV199699032582. A novel 7.6kD allergen from **bee venom**: Isolation and characterization. Astori, M. (1); Kettner, A.; Frutiger, S.; Hughes, G. J.; Corradin, C.; **Spertini, F.** (1). (1) Div. Immunol. Allergy, Cent. Hosp. Univ. Vaudois, 1011 Lausanne Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp. A1479. Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for

Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

L9 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1995:383183 Document No.: PREV199598397483. T cell response to **bee venom** allergens: Modulation by specific immunotherapy. Kammerer, R. B. (1); Chvatchko, Y. (1); Kettner, A. J.; Corradin, G.; **Spertini, F.** (1) Div. Immunol. Allergy, CHUV, Lausanne Switzerland. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 436. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the

L9 ANSWER 19 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1995:381846 Document No.: PREV199598396146. T-cell and IgE response to
partially purified **bee venom** (BV) allergens. Kettner,
A. J. (1); Chvatchko, Y.; Kammerer, R. B.; Corradin, G.; Spertini,
F.. (1) Inst. Biochem., Lausanne Switzerland. 9TH INTERNATIONAL
CONGRESS OF IMMUNOLOGY.. (1995) pp. 208. The 9th International Congress
of
Immunology. Publisher: 9th International Congress of Immunology San
Francisco, California, USA. Meeting Info.: Meeting Sponsored by the
American Association of Immunologists and the International Union of
Immunological Societies San Francisco, California, USA July 23-29, 1995
Language: English.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 14:17:34 ON
16 JUL 2001

L1 7518 S BEE VENOM
L2 502 S L1 AND POLYPEPTIDE
L3 0 S L2 AND 8 KD
L4 55 S L2 AND 8
L5 3 S L4 AND KD
L6 2 DUP REMOVE L5 (1 DUPLICATE REMOVED)
L7 414 S SPERTINI F?/AU
L8 45 S L7 AND BEE VENOM
L9 19 DUP REMOVE L8 (26 DUPLICATES REMOVED)

=> s l4 and IgE binding

4 FILES SEARCHED...

L10 4 L4 AND IGE BINDING

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PROCESSING COMPLETED FOR L10

L11 1 DUP REMOVE L10 (3 DUPLICATES REMOVED)

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L11 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
92113252 Document Number: 92113252. PubMed ID: 1730869.
Glycosylation-inhibiting factor from human T cell hybridomas constructed
from peripheral blood lymphocytes of a **bee venom**
-sensitive allergic patient. Thomas P; Gomi H; Takeuchi T; Carini C;
Tagaya Y; Ishizaka K. (La Jolla Institute for Allergy and Immunology, CA
92037.) JOURNAL OF IMMUNOLOGY, (1992 Feb 1) 148, (3) 729-37. Journal
code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States.
Language: English.
AB Human T cell hybridomas, which constitutively secrete glycosylation
inhibiting factor (GIF), were constructed from PBL of an allergic
individual who was sensitive to honey **bee venom**. PBMC
of the patient were stimulated with either denatured or cyanogen
bromide-treated **bee venom** phospholipase A2 (PLA2), and
Ag-activated cells were propagated by IL-2 in the presence of human
recombinant lipocortin I. T cells obtained in the cultures were fused
with

a HAT-sensitive mutant of the human lymphoblastoid cell line CEM. Approximately one-third of hybridoma clones constitutively secreted GIF. The GIF-producing hybridomas were CD3+ and bore TCR-alpha beta. GIF formed by unstimulated hybridomas lacked affinity for **bee venom** PLA2. Upon cross-linking of CD3, however, a majority of the GIF-producing hybridomas formed **IgE-binding** factors and GIF, the latter of which had affinity for **bee venom** PLA2. Both nonspecific GIF and Ag-binding GIF from the hybridomas bound to an immunosorbent coupled with the anti-lipomodulin mAb 141-B9. Using an affinity-purified GIF as an immunogen, we established mouse B cell hybridomas that secreted monoclonal anti-human GIF. In order to characterize human nonspecific GIF, one of the GIF-producing hybridomas was adapted to a serum-free medium, and culture supernatant was fractionated by DEAE-Sepharose column chromatography and by gel filtration. The majority of nonspecific GIF in the culture supernatant was recovered from DEAE-Sepharose by elution of the column with 10 mM Tris-HCl buffer, pH 8.0, containing 50 mM NaCl. Affinity-purification of GIF in the DEAE Sepharose fraction by using anti-GIF-coupled Affigel, and analysis of the purified GIF by SDS-PAGE revealed that human GIF is a single **polypeptide** chain of 14 to 15 kDa. Gel filtration of both crude and affinity-purified GIF preparations confirmed the molecular size of the cytokine.

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